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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

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December 12, 2017
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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M E E T I N G

(8:00 a.m.)

DR. RAO: Good morning, everyone. I would like to call this meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee to order.

My name is Raj Rao. I'm an orthopedic surgeon with specialization in spine surgery. I'm Chair of the Department of Orthopaedic Surgery at the George Washington University Hospital and university.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by the Barricaid Anular Closure Device by Intrinsic Therapeutics.

I want to give a brief idea of how today will work so that for those of us on the Panel who are new, we get an idea of how the day is going to flow. There will be an initial panel -- initial Sponsor presentation followed by a brief period of time for any preliminary questions the Panel may have and any requests for information that the Panel may have for the Sponsor to bring back for the afternoon session. That will be followed by an initial FDA presentation followed by a brief period of time wherein you can ask some preliminary questions or ask the FDA to bring back any information for more in-depth discussion in the afternoon. This will be followed by lunch. Thereafter, there's time for public comments and there are, I believe, three -- one member of the public so far. That will be followed by a more in-depth discussion by the Panel, and thereafter, we'll go over the FDA's specific questions and try and provide some input on these FDA-related questions, followed by the

vote.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And let me begin with this side of the table.

MS. SCHWARTZOTT: Hi. I'm Jennifer Schwartzott, and I'm the Patient Representative.

MS. STAROWICZ: Good morning. My name is Sharon Starowicz, and I'm Director of Regulatory Policy Innovation for Johnson & Johnson, with responsibility for our global orthopedics businesses, and I am the Industry Rep on the Panel today.

MS. RUE: I'm Karen Rue. I'm from Lafayette, Louisiana, and I own Griswold Home Care, a home care company, and I'm the Consumer Representative.

DR. SAYEED: Dr. Yusef Sayeed. I'm an occupational medicine and interventional pain physician at the Veterans Administration in Battle Creek where I am Chief of Employee Health and Interventional Pain. Thanks.

DR. GILBERT: Good morning. I'm Jeremy Gilbert. I am the Hansjörg Wyss Endowed Chair for Regenerative Medicine and Professor of Bioengineering at Clemson University, Director of the Bioengineering Program at Clemson and Medical University of South Carolina, Professor of Orthopaedics at MUSC, and my area of expertise is biomaterials.

DR. WEISBRODE: I'm Steven Weisbrode, veterinary pathologist, Emeritus Professor at Ohio State University, specialty in veterinary orthopedic pathology.

DR. ELDER: I'm Dr. Benjamin Elder, Assistant Professor of Neurosurgery, Orthopaedics, and Bioengineering at Mayo Clinic in Rochester. My expertise is in spinal surgery as well as bone and cartilage tissue engineering.

DR. BARON: Dr. Eli Baron. I'm an Associate Professor of Neurosurgery at Cedars-Sinai Medical Center in Los Angeles. I'm fellowship trained in both orthopedic and

neurosurgical spine surgery.

DR. SMITH: Harvey Smith, Assistant Professor of Orthopaedic Surgery and Neurosurgery at the University of Pennsylvania, and I'm also at the Philadelphia VA Medical Center in Philadelphia.

CDR ANDERSON: Sara Anderson. I'm the Designated Federal Officer for this meeting. Thank you.

DR. WANG: I'm Marjorie Wang, and I'm from Milwaukee, Wisconsin, Medical College of Wisconsin. I'm Professor and Vice Chair of Neurosurgery and fellowship trained in spine surgery.

DR. KATZ: Good morning. My name is Lee Katz. I am a Professor of Diagnostic Radiology and Orthopaedic Surgery at Yale University.

DR. KIM: My name is Dr. Bong-Soo Kim from Temple University in Philadelphia. I'm a neurosurgeon, and I'm practicing spine surgery.

DR. EVANS: Good morning. Scott Evans, biostatistics at Harvard.

DR. SUBHAWONG: I am Ty Subhawong, Associate Professor of Clinical Radiology at the University of Miami.

DR. DONSHIK: Jon Donshik, orthopedic surgeon, fellowship trained in spine surgery, in private practice in South Florida.

DR. GRAF: Good morning. I'm Carl Graf from the Illinois Spine Institute in Chicago. My expertise is spinal surgery.

DR. FINNEGAN: I'm Maureen Finnegan. I'm an orthopedic surgeon at UT Southwestern in Dallas.

MR. MELKERSON: I'm Mark Melkerson, Director of the Division of Orthopedic Devices at FDA's Office of Device Evaluation.

DR. RAO: Thank you, all. I just noticed two of the microphones, the volume was a

little bit low: Dr. Gilbert and Dr. Kim. So either IT or the individuals may need to speak into their microphones a little bit louder.

Members of the audience, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Commander Anderson, the Designated Federal Officer for the Orthopaedic and Rehabilitation Devices Panel, will now make some introductory remarks.

CDR ANDERSON: Good morning. The Food and Drug Administration is convening today's meeting of the Orthopaedic and Rehabilitative Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened

for potential financial conflict of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalty; and primary employment.

For today's agenda, the Panel will discuss and make recommendations and vote on information regarding the premarket application for the Barricaid Anular Closure Device by Intrinsic Therapeutics. The proposed indication for use, as stated in the PMA, is as follows: The Barricaid is intended to be implanted following a limited discectomy, to prevent reherniation and the reoccurrence of pain or dysfunction. The Barricaid is indicated for patients with radiculopathy (with or without back pain), a posterior or posterolateral herniation, characterized by radiographic confirmation of neural compression using magnetic resonance imaging, and a larger annular defect (e.g., between 4-6 mm tall and between 6-12 mm wide) post-discectomy, at one level between L4 and S1.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Note for the record: Dr. Kimberly Amrami aided the Center's Division of Orthopedic Devices in its review of this PMA submission by serving as an expert reviewer for musculoskeletal radiology. Dr. Amrami is a special Government employee and member of the Orthopaedic and Rehabilitation Devices Panel. Dr. Amrami will be giving a presentation only and will not be participating in the Committee's deliberations. Nor will she vote on the

matter before the Committee.

Sharon Starowicz is serving as the Industry Representative, acting on behalf of all related industry. She is employed by Johnson & Johnson.

We'd like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they might have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript. Thank you.

I will now read the Appointment to Temporary Voting Status Statement.

Appointment to Temporary Voting Status: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Orthopaedic and Rehabilitation Devices Panel for the duration of this meeting on December 12th, 2017:

Dr. Benjamin Elder, Dr. Bong-Soo Kim, Dr. Carl Graf, Dr. Jon Donshik, Dr. Lee Katz, Dr. Marjorie Wang, Dr. Steven Weisbrode, Dr. Ty Subhawong, and Dr. Yusef Sayeed.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have received the material to be considered at this meeting.

Note: Dr. Hollis Potter is unable to attend the meeting.

This has been signed by Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on December 7th, 2017.

For the duration of the Orthopaedic and Rehabilitation Panel meeting on December 12th, 2017, Ms. Jennifer Schwartzott has been appointed to serve as a Temporary Non-Voting Patient Representative. For the record, Ms. Schwartzott serves as a consultant to the Cellular Tissue and Gene Therapeutics Advisory Committee in the Center for Biologics Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the materials to be considered at the meeting.

This appointment was authorized by Rachel Sherman, M.D., Associate Deputy Commissioner, Office of Medical Products and Tobacco, Office of the Commissioner, Food and Drug Administration, on November 20th, 2017.

Before I turn the meeting back to Dr. Rao, I'd like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (410) 974-0947.

Information on purchasing videos of today's meeting can be found at the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today is Theresa Eisenman, and if available, please stand up for the crowd. She's waving. Thank you.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded. Repeat: I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you'd like to present during today's Open Public Hearing session, please register with AnnMarie Williams at the registration desk.

All written comments have been included in the panelists' folders and have been reviewed. A copy of the statements received may be viewed at the registration table.

In order to help the transcriptionist identify who is speaking, please be sure, panelists, to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Rao.

DR. RAO: Thank you. We will now proceed to the Sponsor's presentation. I would like the Sponsor to approach the podium.

I will remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 90 minutes to present. You may now begin your presentation. It's 8:18. Thank you.

MR. HAGAN: Thank you. Good morning, my name is Cary Hagan, and I'm president and CEO of Intrinsic Therapeutics. We're looking forward to today's discussion. I would like

to thank the FDA and the Panel for their time and review of the safety and effectiveness data supporting the Barricaid Anular Closure Device.

For more than a decade, Intrinsic has been solely focused on solving the challenge of reherniation following discectomy. Our commitment stems from the founder's personal experience, a family who became permanently disabled as a result of multiple discectomies due to reherniation.

What we know is that discectomy is a safe and highly effective procedure that relieves the pain and disability associated with a herniated lumbar disc. And we also know there is a subset of discectomy patients for whom the risk of reherniation and reoperation is very high. This is the treatment gap that exists today, and our device can improve the outcomes of patients' lives by reducing the rate of repeat back surgery.

What we and others have learned is that high-risk patients are those that have an annular defect following discectomy that is at least 6 mm wide, and it's this group of patients for whom the Barricaid was designed.

Intrinsic has conducted the most comprehensive trial to date for lumbar discectomy, and today we will outline the clinical protocol, the trial design, and the data generated from the Barricaid clinical trial. We will provide data supporting the Barricaid safety, effectiveness, and positive benefit-risk profile, with a very specific focus on radiographic observation.

Every year, 3 to 4 million patients in the United States suffer from disc herniation, nerve impingement, and associated sciatica. Roughly 10% of these sciatica patients undergo discectomy surgery, an estimated 350,000 patients annually. High-risk patients

represent a subset, 30 to 40% of all discectomy patients. These patients have few options today.

We're committed to the 120,000 patients who are at the highest risk for repeat back surgery. These high-risk patients have a 1-in-4 chance of reoperation versus a 1-in-100 chance for reoperation for the remainder of the discectomy population. To be clear, the Barricaid device is not for every patient. It is only for patients who require discectomy and are at high risk.

The Barricaid is intended to block large annular defects with a flexible occlusion component. It maintains the benefits of a discectomy while reducing reherniations and additional surgeries. The device has been CE marked since 2009, and roughly 6,000 patients have been treated worldwide in more than 20 countries.

The study design and protocol were heavily influenced by feedback and interaction with FDA, which began in 2008. A thorough safety evaluation plan was performed over several years to obtain a CE mark outside the United States. The frequency and quality of interactions with FDA and the review team have been beneficial, and FDA's input to the study design has led to the clinical trial protocol and the radiographic assessments that will be presented here today.

Here's the agenda for the remainder of our presentation. First, Dr. Golish will describe the clinical need and study design. Dr. Bouma will review the safety and effectiveness data, followed by Dr. Kursumovic, who will present the radiographic observations and endplate changes. Both Drs. Kursumovic and Bouma were investigators in the trial. Then Dr. McGirt will provide his insights on the benefits and risks of the Barricaid

Anular Closure Device. And then finally, Glenn Stiegman, from MCRA, will moderate our question and answer session.

We also have additional experts with us today to help answer questions. None of our external speakers have a financial stake, royalty, or equity in either the Barricaid device or Intrinsic Therapeutics. They have been compensated for their time and for their travel.

Thank you. I'll now invite Dr. Golish to the lectern.

DR. GOLISH: Good morning. I'm Raymond Golish, an orthopedic surgeon, spinal surgeon, and medical device scientist based in Palm Beach.

Herniated lumbar disc is a common problem. This image orients you to the lumbar region, and you can see in the illustration at the top right a normal disc with a healthy annulus fibrosus. The image on the bottom right illustrates a herniated disc, which is associated with compromised annulus. It's through this defect in the annulus that nucleus herniates can impinge on the spinal nerves, causing neurologic symptoms.

It's important to note, also, that the lumbar region is typically below the level of the spinal cord and instead in the region of the cauda equina containing the spinal nerve roots.

This is an image of an MRI, which shows extruded disc material in the epidural space impinging on the neural elements causing excruciating sciatica pain and loss of function. For those patients with severe symptoms, having failed all nonsurgical management, a well-done microsurgical discectomy is a great operation, one of the best in all spinal surgery. Odds are someone in this room has recovered from debilitating symptoms after a beautifully done discectomy. Every spine surgeon has relished the professional joy of curing a previously debilitated patient.

However, microsurgical discectomy is not perfect, and a recurrent herniated disc, after a surgery, is a serious and well-recognized problem.

Every surgeon has been disappointed to see a previously thriving patient return with debilitating symptoms, sometimes severe enough to warrant a revision discectomy. For these patients, recurrence is a physically and emotionally morbid event with significant impact on quality of life and time to convalescence.

The top image is an MRI of a herniated disc requiring surgery, after which the patient thrived. The bottom image is a recurrent disc herniation, months later, causing severe recurrent symptoms requiring revision discectomy. The graph shows that the patient improved after the initial surgery, but then pain and disability scores spiked severely at the time of reherniation. This pattern following discectomy is why the Barricaid device was developed and represents a major unmet clinical need. That's why we're here today.

The problem of recurrent herniation is also well documented in the scientific literature. Recurrence rates in the general discectomy population range from 8 to 12%. But these numbers represent all comers with herniations and annular defects of all sizes from small to large. These rates are what we, as surgeons, expect to see in the general post-discectomy population.

However, remember that 30 to 40% of the discectomy population has large annular defects and is at high risk of reherniation.

When we break out this high-risk population, the reherniation rate is 2½ times higher in patients with large annular defects, as concluded in a recent meta-analysis of over 1,600 patients and in the example of a Carragee study, shown in red.

Similarly, with reoperations due to reherniation, rates in the general discectomy population range from 5 to 11%. But again, these numbers represent all comers with herniations and annular defects of all sizes.

Restricting the analysis to publications of patients with large defects, we see a much different picture. Patients with large annular defects are at much higher risk for reoperation due to reherniation. The meta-analysis shows a more than doubling of the risk of reoperation in these patients.

And these reoperations are not just single, transitory events. Failure of discectomy carries with it considerable consequences and often changes the trajectory of a patient's prospects for the worse. As surgeons, we remember these patients and their chronic suffering. Reoperated patients have significantly less functional improvement and a correspondingly low rate of overall satisfaction. These patients are much more likely to use opioid medication and at elevated doses. A recent large study from Ohio illustrates how reoperated patients are challenged to return to gainful employment. Patients with larger annular defects at the time of their initial discectomy are then at an elevated risk of having to deal with this chronic disability.

Let's take a closer look at these larger annular defects. The image on the left is intended to give you an idea of defect dimensions, and the image on the right depicts the Barricaid device in position with the disc nucleus in front of the occlusion component and the annular wall behind it. By mechanically blocking the defect, Barricaid can prevent future reherniations and the subsequent reoperations.

The Barricaid implant has two main components: the occlusion component and the

titanium anchor. The occlusion component closes the annular defect. It's made of multilayered, woven, flexible, non-biodegradable Dacron. There's also a radiopaque marker to ensure visibility under fluoroscopy. Note that the occlusion component is not rigid or load bearing and is designed to allow for dynamic motion as the patient resumes normal daily activities. The occlusion component is thermally secured to a titanium alloy anchor that affixes the implant into the bone of the vertebral body, and Dacron and titanium are both common biomaterials used in permanent implantable devices.

The Barricaid implant is preloaded onto a single-use disposable tool that allows precise and controlled delivery. We have zoomed in on the device here to better appreciate the size, which is available in three occlusion component widths -- 8, 10, and 12 mm -- to accommodate different defect sizes. The anchor is identical for all the implants, independent of the width of the occlusion component. The width of the annulus defect determines which Barricaid size is selected. The physician is instructed to select an occlusion component no smaller than the defect width.

A thorough safety evaluation plan was performed over several years to obtain the CE mark outside the United States:

First, to create the foundation for the Barricaid safety profile, extensive mechanical testing was performed out to 10 million cycles in worst-case models, or were designed to create failure in fewer cycles.

Second, a 6-month small mammal model demonstrated lack of neurotoxicity due to implant materials. A 12-month primate study established the integrity of the device with no fractures or migrations and further demonstrated the biocompatibility of the device with no

systemic toxicity.

While there was evidence of inflammation around the device, the study pathologist concluded that inflammation around the fabric was only evident after the endplate was disrupted with pro-inflammatory cytokines at all time points in the controls as well. This observation is also documented in the literature.

There were limitations in the primate study contributed to by the device size mismatch relative to the experimental model, as the disc space was roughly the same as the occlusion component thickness.

Lastly, the device performance was evaluated in a human cadaveric implantation study to validate the surgical technique, and a pilot clinical study with 30 patients established this initial safety profile.

The totality of these studies demonstrate a reasonable assurance of safety that supported initiation of the randomized clinical trial.

Let me walk you through the insertion technique. The insertion technique is straightforward. A discectomy is first performed, employing standard surgical technique. The herniation is accessed by performing a hemilaminotomy. The offending fragment is removed. The annular defect is then identified and measured using specialized instruments to assess if the patient is indicated for the Barricaid.

In the trial, once the defect size was confirmed to be 6 mm or wider, patients were randomized only then, using a web-based platform. Up until this point, the patient has only received a standard discectomy ,and patients had to meet this final inclusion criterion of defect size intraoperatively.

Next, fluoroscopy is used to ensure proper positioning of the device. The inserter, which is preloaded with the appropriately sized device, is placed against the back of the vertebral body with protection of the neural elements, and a specific bone preparation is required prior to implantation. Tapping on the strike cap on the back of the inserter with a surgical mallet simultaneously drives the anchor into the vertebral body while deploying an advancing occlusion component in front of the defect. The instrument is designed to limit the implantation depth to the desired 2 mm.

The implant is now completely seated with the occlusion component covering the annular defect. And again, fluoroscopy is used to ensure precise alignment and placement. Depending on the location of the defect, the Barricaid device can be implanted in the inferior vertebral body, as we just saw, or the superior, as shown here. Finally, the wound is closed using standard technique.

All patients in this study were treated with modern discectomy technique, which involves conservative removal of the offending disc material. To access the disc, the rent in the annulus due to the herniation itself was found and exploited whenever possible. When necessary, a limited annulotomy was performed only as large as necessary for a full and satisfying decompression of the compressed nerves. As with prior literature linking defect size to reherniation risk, the size and shape of the defect was assessed after the discectomy was complete.

The proposed indication for the Barricaid device is for patients with radiculopathy and a posterior or posterolateral herniation, characterized by imaging confirmation of neural compression using MRI, and a large annular defect post-discectomy, at one level

between L4 and S1.

You've received information on the safety and effectiveness of the 12 mm device in your panel pack.

We want to be clear to the Panel on the study population. This device is not intended to be implanted in every discectomy patient. The consensus and the totality of the scientific literature, and a recently published meta-analysis, is that defect size greater than or equal to 6 mm is a clear risk factor for reherniation and secondary surgical interventions.

This study enrolled the specific patient population who are identified during surgery, and the procedure used in both arms was a limited discectomy, representing modern standard microsurgical technique.

Next, I'll review the Barricaid study design. The safety and effectiveness of Barricaid was evaluated in a multicenter, pivotal, two-arm randomized controlled trial. Patients were randomized 1:1 intraoperatively after discectomy and confirmation of the defect size to isolate the at-risk subpopulation without selection bias. Superiority was defined prospectively with Barricaid compared to lumbar discectomy alone.

The trial had two co-primary endpoints: a reherniation endpoint as well as a composite endpoint with eight individual components. These co-primary endpoints make for a very high bar compared to previous spinal pivotal device trials. The trial also included an extensive radiographic protocol.

Prior to surgery, patients had history, physical exam, completed patient-reported outcomes, and had imaging taken, including plain radiographs, MRI, and low-dose CT.

Subjects were seen postoperatively at 6 weeks; 3, 6, and 12 months; and annually thereafter to 5 years. Again, physical exam, patient-reported outcomes, and plain radiographs were obtained at every time point. MRI and CT were obtained annually.

It's important to recognize the extensive imaging analysis in this trial, yielding a tremendous quantity of information. The images on this slide are examples from the Barricaid population at the same time point. As you can see in the middle image, Barricaid does not interfere with MRI image quality.

The assessment of recurrent herniation in this study was also exhaustive, and every MRI taken at each annual time point and at unscheduled visits was assessed by at least two radiologists for each element listed here.

To be included in the study, patients had to be between 21 and 75 years old with a large defect between 4 and 6 mm tall and 6 to 10 mm wide, measured intraoperatively following completion of the discectomy. Patients were also required to have a minimum disc height of 5 mm and at least 6 weeks of failed conservative treatment.

These inclusion criteria allowed for the enrollment of the typical herniation patients presenting with posterior or posterolateral lumbar disc herniation and radiculopathy, similar to the general discectomy population.

These are the key exclusion criteria used to screen patients for the trial, which are typical criteria for spinal pivotal device trials.

This study had rigorous independent oversight that included medical ethics committee oversight and independent histopathology and radiographic core labs. To level set all the imaging assessments, the core lab read all radiographs and was responsible for

evaluating the endpoints of reherniation, device integrity, and disc height. Two U.S. board-certified radiologists reviewed and assessed each image, with a third available for adjudication, if needed. An independent data safety monitoring board, made up of three U.S. board-certified spine surgeons and one board-certified radiologist, adjudicated all the adverse events.

This study was designed with two co-primary endpoints assessed at 24 months, which required statistical superiority of Barricaid over control for each of the two endpoints independently.

The first endpoint is radiographic reherniation. To be considered a success here, the patient must have no evidence of recurrent herniation at the index level any time up to and including the 24-month follow-up visit. The core lab reviewed any MRI for the evidence of reherniation, and reherniations could also be confirmed surgically. Both asymptomatic reherniations and contralateral herniations were included, during collaboration with FDA, to assess the device's mechanism of action.

The second co-primary endpoint is a composite of safety and effectiveness endpoints typical of pivotal device trials. To be considered a success here, patients needed to meet all eight binary criteria seen here, an extraordinarily high bar. The value of the strict composite definition is that it ensures that superiority is specifically driven by the device's mechanism of action and its biomechanical rationale.

Let's look at the components of the composite. We grouped each of the eight components of the endpoint based on the type of assessment to ensure a complete picture of the impact of the device. Those assessments that were specific to the effectiveness of

the discectomy procedure were VAS, ODI, and neurologic status. The positive impact of decompressing the nerves occurs during discectomy, so we might expect these measures should be at least similar between the arms.

Similarly, the spontaneous fusion and disc height components were radiographic assessments that characterized motion preservation and progression of spondylosis, respectively. We should expect that the results would be similar between the arms.

However, the last set of assessments are those specific to the safety and efficacy of the Barricaid device: reducing reherniations and reoperations and maintaining the condition of the device. The study was designed to demonstrate Barricaid's superiority to control on these components and for these components to drive the overall superiority of the composite.

Thank you. I'd now like to invite Dr. Bouma up to the podium to share the study results.

DR. BOUMA: Thank you, Dr. Golish.

Good morning. My name is Gerrit Bouma. I'm head of the Department of Neurosurgery at the OLVG Hospital in Amsterdam, the Netherlands, and I'm one of the investigators on the Barricaid ACD.

This study was conducted at 21 sites in Tier 1 countries in northwest Europe, and by a total of 46 orthopedic and neurosurgeons. Together, we screened over 3,300 patients, a fifth of whom were eventually enrolled. Of the 3,332 patients screened for the initial -- for this study, 647 patients met the initial inclusion criteria and went to surgery.

The main reasons for preoperative exclusion were lack of patient consent, an

insufficient period of conservative care, prior surgery at the index level, or a low posterior disc height.

During the intraoperative screening, another 93 patients failed inclusion primarily due to defect size, leaving 554 patients, or 17%, of the screened patients that were randomized; 278 were randomized to the control group and 276 to the Barricaid group.

In four patients who were randomized to Barricaid, no implantation attempt was ever made because of apparent anatomic limitations. That leaves us with 272 patients in the modified intent-to-treat, or mITT, patient population, which represents all patients in whom the intended procedure was attempted. This is the main population for the effectiveness analysis.

All patients are past the 2-year visit, with data available for 245 Barricaid and 259 control patients. Accountability was high in both groups, at more than 90% at the primary 2-year follow-up time point.

As mentioned, effectiveness analyses were performed on the mITT population, where patients were included in cohorts to which they were assigned at randomization. When we transition to safety, we used the as-treated population, as requested by the FDA, defined as being the actual treatment that a patient received.

Five patients who were randomized to Barricaid and in whom implantation was attempted ended up not having -- not receiving the device and were treated with a standard discectomy, like the control patients. One of these patients had a defect that was too medial, another one experienced a nerve root injury, and there were three instances where the mesh would not fully enter the disc space. These five patients are in the

Barricaid group for the mITT analysis but in the control group for the as-treated analysis.

As you would expect in a well-randomized study, there were no significant differences between groups with regard to demographics. The study is a typical primary discectomy population, young, with a mean age of 43 and predominantly male with a high level of preoperative pain and functional impairment and mainly at the lowest two lumbar levels.

Similarly, intraoperative characteristics were balanced between groups. The mean defect size was approximately 8 mm in width and 5 mm in height. And discectomies were nearly identical, involving nucleus removed.

As expected, the added step of implanting the Barricaid device resulted in longer operative times. This difference, however, had no impact on the outcomes that we are going to present to you today.

There has been a lot of discussion regarding annulotomies and defect geometries. It should be noted that only one-third of all defects were actually created by the surgeon, whereas in two-thirds of the cases discectomy was performed through the existing defect.

The shape of the defect was classified after the discectomy. In most cases, this was assessed by the surgeon as being box shaped, but this does not mean that a box annulotomy had also been performed. In my experience, if the defect was irregularly shaped, as it typically was, I most often chose box just for lack of a better alternative.

We looked closely at each of these parameters, that is, whether the defect was new or existing and the geometry of the annular defect as recorded by the surgeon during surgery, and these parameters had no impact on any of the outcomes that you will hear

about today, including the primary endpoints, as well as reoperations and symptomatic reherniations.

Now, let me tell you about the primary endpoint results. The Barricaid group was superior to control in both pre-specified co-primary endpoints, with both posterior probabilities greater than 99%. This was achieved at 2 years, which is consistent with other recent spine trials and as a common surrogate for device safety for PMAs.

The Barricaid's mechanism of action was demonstrated by preventing reherniation better than control. Barricaid was also superior in the composite endpoint of safety and effectiveness.

We performed a comprehensive exploratory analysis to evaluate the impact of differences in baseline and intraoperative characteristics, seen here, to see if any of these characteristics influenced the treatment outcome at 2 years. These exploratory analyses demonstrated that differences in these characteristics have no impact on clinical outcome.

In addition to the primary study endpoints, it is also valuable to look at the individual components of the composite endpoint. As expected, the Barricaid group was similar to the control group in both the discectomy-specific measures and the general radiographic outcomes, demonstrating that addition of the Barricaid device does not diminish the positive impact of the discectomy. On the other hand, Barricaid was superior to control with regard to reherniation and reoperation.

As a reminder, patients had to be successful in all eight of these subcomponents in order to be a success on the co-primary composite endpoint.

Importantly, Barricaid was superior to control in device-specific safety and

effectiveness measures as a group, despite the occurrence of device integrity issues which were outweighed by the reduction in reherniations or secondary surgical interventions.

Next, I will step through the discectomy radiographic- and device-specific buckets in more detail. First, let's take a closer look at the discectomy-specific components, which, as expected, performed similarly in both groups.

Here are the mean VAS scores over time. Note how far the results exceed the minimal clinically important difference, or MCID. The Barricaid device was similar to control in relieving leg pain. Both groups experienced meaningful improvements in reduction in leg pain from baseline through 5 years.

Barricaid was also similar to control with regard to ODI improvement, with both groups far exceeding the MCID again. Both groups experienced meaningful improvements in pain and function from baseline through 5 years.

One question I often receive is whether Barricaid implantation might lead to greater neurological issues. I have not seen this problem in my clinical practice, although across the study, there have been a few observations of neurologic deterioration occurring in both treatment groups, but overall, both groups performed similarly well through 5 years of follow-up.

Next, let's look at the pre-specified radiographic components of the co-primary endpoint. Keep in mind that Dr. Kursumovic will follow my presentation with a detailed analysis of endplate changes.

Clearly, all patients were free from spontaneous fusion at 2 years, and this was maintained through Year 5. With regard to disc height, a similar percentage of patients

exhibited maintenance of disc height at each time point through 5 years.

Next, we will discuss the safety and effectiveness measures specific to the Barricaid device. This grouping of components consists of terminal failure types, meaning if patients fail at any time, they are failures for all subsequent time points. Because the control group does not have device integrity observations, these events were combined with reherniations and secondary surgical interventions, with any of the three representing failure to evaluate the safety and effectiveness of the Barricaid device.

Barricaid was shown to be superior for this grouping of endpoints, as the reduction in reherniations and reoperations outweighed the radiographic device integrity observations by a margin of 17.6 percentage points with a high degree of significance.

The figure on the left shows the cumulative number of all reherniations that have occurred over time, regardless of symptoms, while the figure on the right presents the cumulative reherniation as estimated through Kaplan-Meier analysis. The number of at-risk patients for the Kaplan-Meier analysis is shown in the table below. A superior margin for Barricaid appeared early and was maintained through 5 years. At 2 years, there was a difference of more than 20 percentage points in favor of Barricaid.

Here is a similar analysis, but for reoperation. Again, a superior margin for Barricaid appeared early and was maintained through 5 years. At 2 years, the estimated failure rate was 8.8% for Barricaid and 16.4% for control, indicating an almost 50% reduction. This is especially significant because patients who are reoperated often go on to have a second, a third, or even a fourth operation. Barricaid patients had a total of 49 reoperations compared to 79 in the control group out to 5 years. We are able to show you these effects

because, unlike many other studies, this study continued to follow patients even after they failed the study endpoint due to reoperation.

Later today you will be asked to vote on the safety of the device. To do so, it's critical to use an analysis that takes into account all available safety events. We've presented survival analysis of the long-term data for the composite endpoint, reherniation, and reoperation because it takes the safety of all patients into account and is therefore a more accurate account of device performance. This type of analysis is also supported by FDA guidance.

A cross-sectional analysis is limited to only those patients theoretically due for each time point and is used if all of these patients have come in for their visit. All terminal failures, like reherniations, are carried forward, but of course, successes are not counted until the patient has come in, so this results in bias against the cohort with a greater proportion of successful patients. Most importantly, in our study, a cross-sectional analysis would ignore more than 60% of all known safety events.

Next, I would like to discuss an actual concern for clinicians, that is, how complicated it is to reoperate on a patient that has been implanted with this device.

Well, reoperations in the Barricaid group were no more complex than in the control group, with no significant differences in operative time in patients undergoing reoperation, either when looking at those treated with a fusion or those treated with decompression only. Further, fewer complications were noted in Barricaid removals and revisions than in reoperations of any type in control.

For all devices that were revised, an extensive retrieval analysis program was in

place. There were 63 retrievals of implants and instruments in all commercial and study experience combined. In the study, there were 25 explants, three of which were immediately discarded by the clinical sites, and another one was returned to the patient upon their request. So 21 explants were retrieved, and all were analyzed per the FDA's accepted standard.

The retrieval analysis concluded that the occlusion component, when it was detached, experienced ductile failure, although it was not always possible to tell if the damage had occurred in vivo or was caused iatrogenically. All retrieved mesh migrations were co-observed with herniated nucleus.

Of the 21 retrievals, 11 had tissue available for histological analysis. Seven retrievals had birefringent particles associated with the device. The analyses were not able to link birefringent particles to EPCs or inflammation since these observations are both present and absent when particles were observed. Similarly, particles were not observed where there was evidence of osteolysis. Histology analysis concluded there was an expected host-implant response with no evidence of infection and no association of inflammation with bone resorption.

Device integrity is an important component of the composite endpoint. Every observation was counted as a failure of the primary endpoint regardless of symptomatology. It has two different and independent aspects. A device condition observation was identified by the core lab if there was a fracture of the anchor or a disassembly of the occlusion component. Migration was defined as greater or equal to -- than to 2 mm of movement relative to the initial anchor position or movement of the

occlusion component beyond the posterior margin of the disc space. This is assessed radiographically by the core lab using a stringent definition without consideration of any clinical information.

There were a total of 32 radiographic device integrity observations within the primary study period. There were five migrations or fractures of the anchor by 2 years and another one after 2 years. Of these, one was a misplaced device, and three are related to bone density or other comorbidities.

The occlusion component had a total of 27 integrity observations at a 2-year time point and 15 beyond 2 years, most of which were migrations still attached to the anchor. Two of these instances at 2 years were cases of an undersized device, which would be mitigated with appropriate adherence to the instructions for use.

Let's look at the impact of the total number of observations seen through 5 years. Many of the device integrity observations are radiographic only and are asymptomatic, as shown by the light blue slice. By asymptomatic, we mean no reoperations, no symptomatic reherniation, ODI and neuro success, and no SAEs.

While symptomatic reherniations can be reduced by over 50% at 2 years with Barricaid, they still can occur. Sometimes, these herniations can even displace the mesh. Symptomatic reherniations have been concurrently observed with occlusion component migrations in 19 of the 48 device integrity observations to date. These events have already been captured as failures of the primary endpoint. The remaining eight observations were solely associated with the device rather than with reherniation. This group represents 3% of the total Barricaid population. One of these patients had neurodegeneration, and one

did not show ODI improvement. However, these patients did not have any secondary surgeries, reherniations, or related SAEs. Three of these patients had SAEs, and another three had a reoperation. Again, these device-attributed risks manifested in 3% in the Barricaid population through 5 years.

As stated previously, the Sponsor met the a priori composite endpoint for superiority.

We also created a more patient-focused composite endpoint. The a priori co-primary endpoints are appropriate for a clinical study to assess safety and effectiveness of a device; they are strict, and they are detailed when considered outside the clinical study context. However, they may not fully reflect patients' and surgeons' expectations of discectomy. The explanation for this discrepancy is the inclusion of radiographic observations in each of the co-primary endpoints that do not necessarily have any clinical relevance.

Therefore, a patient-focused composite endpoint was proposed. This endpoint was not intended to replace the pre-specified co-primary endpoints, but rather to better capture the clinical success rates of both study populations from a surgeon's and patient's perspective. This endpoint also aligns with composite endpoints used in other spine PMAs.

The components of the patient-focused endpoint are ODI improvement, no neurologic deterioration, no symptomatic reherniation rather than no reherniation at all, no secondary surgical interventions, and no device- or procedure-related SAEs.

Note that the impact of device integrity observations is captured with the addition of the related SAE component.

Here are the results for the two co-primary endpoints we already showed, now with an added row for the post hoc, patient-focused composite definition. We can see that the treatment differences are similar in size, and all endpoints retain statistical significance in favor of Barricaid, as was observed in the a priori definition.

In the patient-focused composite, the success rates were more typical of the success rate in this high-risk subset of the discectomy population. Even if VAS leg was used instead of or in combination with ODI, it would not have changed the outcome.

Next, let's look at each of the components in more detail, starting with symptomatic reherniations. Symptomatic recurrent herniations were identified either at reoperation or after reherniation was radiographically confirmed by the independent core lab. If the image was from an unscheduled visit, the event was classified as symptomatic.

If the image was from a regular follow-up visit during which a standard neurological exam was completed, one of the following had to be true for a reherniation to be considered symptomatic:

- First, there was either an adverse event reported for an index-level reherniation that required treatment, or an adverse event was reported for a lower extremity or lumbar pain or neurological event within 1 month of imaging.
- Second, the patient's leg pain function and neurologic scores would have met the inclusion criteria again for the study. That means VAS above 40 or ODI above 40.

All reherniations that did not meet the above criteria were considered to be

asymptomatic.

As expected, the majority of symptomatic reherniations were confirmed at surgery, and the proportion of patients identified through other pathways were similar in each cohort. So this algorithm created a broad net which captured any symptomatic reherniation while avoiding the bias associated with relying solely on investigator reporting.

Critically for the patient, Barricaid was superior to control in terms of symptomatic recurrence. Again, the superior result appears early and is maintained through 5 years. At 2 years, the estimated symptomatic reherniation rate for control was 25.5%. This is similar to what has been presented in the literature for the large defect population, as represented by the red circle. The rate from Barricaid was 11%, less than half of the rate of symptomatic reherniations observed in the control group.

Critical to understanding the impact of any therapy is the review of the adverse event data and particularly those events that are serious, that is, they require hospitalization or surgery, and those events that are related to the device or the procedure.

Here is a summary of the adverse events in our study. The only statistical difference was in SAEs that were related to either the device or the procedure, with fewer such events in the Barricaid group despite the presence of the device. The events caused by the device are more than outweighed by the reduction in events associated with reherniations. These data suggest that discectomy plus Barricaid has a better safety profile than discectomy alone. In fact, the cumulative time incidence of device and/or procedure-related SAEs show a stable trend in favor of Barricaid through 5 years.

Similarly, and as presented earlier, Barricaid was superior to control with respect to

the reduction of reoperation. It's important to emphasize that reoperation is not a single burdensome and risky event. Patients who required reoperation following discectomy fared worse than patients who did not. ODI, VAS leg, and VAS back greater than 40 at 2 years and the presence -- and the percentage of patients who are not working are all measures of significant disability.

These light blue bars represent Barricaid and control patients combined, who required a second surgery in the study and met the criteria for disability I just mentioned.

Now, compare these data to those who did not require a second surgery, represented by the dark blue bars. There's a two to threefold increase between groups. So these data reinforce that reoperation carries a significant consequence in increased pain-related disability. More than 40% of patients were no longer working following a reoperation. These reoperations are life-changing events that Barricaid can attenuate.

In summary, the Barricaid device has demonstrated superiority to control.

It has met both co-primary endpoints per the protocol, as well as the more patient-focused ultimate composite endpoint.

Importantly, Barricaid was superior to control with regard to symptomatic reherniations, reoperations, and related SAE outcomes that are critical to the evaluation of benefit and risk of this new procedure and to any patient success.

Thank you. I will now invite Dr. Kursumovic to the lectern.

DR. KURSUMOVIC: Thank you. Good morning. My name is Adisa Kursumovic, and I am a practicing neurosurgeon in Deggendorf, Germany. I have extensive experience with the Barricaid device, having been among the first commercial users when it was first

introduced in Europe in early 2009. My colleagues and I in Deggendorf have implanted over 250 devices since then, in addition to the 40 patients we enrolled in the study we are discussing today. I follow all of my Barricaid patients with imaging taken about a year after surgery, and as a result of this prospective imaging, I was among the first to identify the endplate changes, or EPCs, in those implanted with Barricaid. Therefore, I'm pleased to be here today and to share the extensive research we have done on this topic.

Before we jump into the details of what we saw in the study, it's important to understand what the endplate is. On the top and bottom of every vertebra, at the point where the vertebra meets the disc is a layer of bone covered by cartilage. Anatomically, the endplate cortex is less than a millimeter in thickness and is typically thinnest at the center to promote a nutrition pathway to the disc. Endplates often flex in response to loading and can present in a variety of curvature and shapes.

We know from the literature that endplates degenerate naturally over time, even without a discectomy. An increase in endplate changes following the discectomy type procedures is expected, regardless of whether or not an annular closure device is used.

The top image is an unaffected endplate. The bottom image from a control patient is an endplate change after discectomy. In the study's radiographic protocol, this was defined as any osseous disruption of the endplate, including cavities that might extend further into the vertebral body. These radiographic observations have been described most often in the literature as endplate changes and less often as endplate lesions, though the distinction remains unclear. For the purposes of this presentation, we will use the term "endplate changes" to describe these radiographic findings. Some sites have chosen to

report these symptomatic EPCs as bone necrosis or resorption, as this was the only AE code available. Just to be clear, all sites reported EPCs are already captured in the core lab radiographic findings.

The literature and medical teaching tells us that visible defects in the endplates are accepted to have no clinical consequence for most people.

Here is an x-ray, MRI, and CT of endplates in the same patient. You can see how easily identifiable the changes are in CT versus the other modalities. Endplate changes post-discectomy are not a new phenomenon but are rarely observed as postoperative images, and particularly, CT is not usually done in this study.

Longitudinal CT imaging in this study revealed the greater prevalence of endplate changes in a normal discectomy population than has been previously described in the literature. The prospective nature of this study, the use of an independent core lab with multiple readers, and the extensive protocol of assessments makes the study uniquely positioned to enable conclusions regarding the stability, progressiveness, and radiographic features of such endplate changes.

Endplate changes can take on a variety of shapes and sizes. They were observed in both groups, and representative images are shown here, with EPCs indicated by the yellow arrows. All of these images were taken at 1 year postop.

Prior to detailing the specific methods and analyses that were utilized to investigate EPCs, I want to summarize the key findings.

Endplate changes were observed in both groups. While they were more frequent and larger in average size in the Barricaid group, the range of sizes was similar between

groups. Larger endplate changes grow more slowly and plateau at the size at which there is no risk to the vertebral body integrity. And finally and most importantly, the analysis demonstrated no evidence of any negative clinical impact associated with Barricaid and endplate changes.

Now I will detail the radiographic assessments and analyses that were performed to support these conclusions.

Quantitative size data, location tracking, and qualitative assessment of the endplate change appearance were performed by the independent radiographic core lab to best understand and characterize the endplate changes in our study.

More than 50,000 radiographic images were collected to extensively assess endplate changes. These data allow Intrinsic to truly understand the characteristics of EPCs, the qualitative features, and most importantly when endplates stabilized.

Combining both qualitative and quantitative features captures endplate change stability from both the sample size measurement and the physiologic human response. Evaluating both provides a true and thorough sense of stability.

Additionally, we performed a variety of analyses in an attempt to correlate clinical outcomes to endplate change presence or type.

And finally we performed all of these analyses for the overall population as well as for several subgroups, including those identified by FDA. These subgroups included endplate changes with mesh subsidence beyond the cortex and endplate changes that were larger than 100 millimeters clear, which is roughly the upper 20% of endplate changes in terms of size. FDA describes the group of endplate changes in which the mesh has subsided

as lytic and has understandably expressed concern about this group. We will present stability and correlation data for several subgroups with a focus on this one in particular. These assessments and analyses facilitate detailed understanding of endplate changes following discectomy with and without annular closure.

As shown in these images from a control patient, size was measured in the sagittal, coronal, and axial planes where the EPC appeared largest, employing a methodology that has been reported in the literature. Throughout this presentation, area measurements reflect the averages of the EPC size in each of the three planes. A separate study demonstrated that this measure was well correlated with volume measurements performed with 3D reconstruction of the CT slices. Over 100 EPCs representing the full range of sizes were included in this separate study.

Next, I will detail some of the results of these analyses.

FDA will be asking you whether there is any current or future clinical impact of EPCs and if any additional analyses should be conducted. We have tried to look at these data in every way possible to answer questions about etiology and clinical relevance.

In total, there were 483 endplate changes among 235 Barricaid patients and 190 endplate changes among 113 control patients. There was a postoperative increase in number of observed endplate changes in both arms of the study. Interestingly, endplate changes were observed preoperatively, indicating that the herniation itself might sometimes be associated with these changes. The range of EPC size was similar between groups, with the largest endplate change actually being observed in the control group.

We tried to understand why these EPCs were occurring and why they were more

frequent in the Barricaid group. There were two primary sources of data that helps to establish root cause. First, the imaging appearance is not consistent with infection or particle-induced osteolysis. Second, histology from the explanted devices demonstrate a lack of active osteolysis.

The cause of EPCs appears to be mechanical in nature. Preoperatively, EPCs can be driven by the herniation itself, which often includes fragments of the endplate. Postoperatively, EPCs can develop as a result of the discectomy procedure or loss of disc material. The nucleus only has two places to go, through the annular fissure or through the cartilaginous endplate. Barricaid prevents reherniation by occluding the annulus, and therefore, there might be a greater propensity to go through the cartilaginous endplate or to push the occlusion against the endplate, which will then retreat with the mesh coming to rest within the resulting defect.

There was a similar root cause for humans and baboons, whereby a mechanical disruption to the disc space caused a tissue reaction. The response was more pronounced in baboons due to the occlusion component being the same thickness as the disc space. EPCs were also seen in the control sites, though to a lesser extent.

While the root cause is important to understand, let me show you our 5 years' human data that demonstrate EPCs stabilize and have no clinical impact.

In terms of change in size over time, we observed that larger EPCs grow more slowly, regardless of treatment arm. In these graphs, the x-axis is the size of the EPC, and the y-axis is the change in size in the next year. The y-axis has both positive and negative values indicating both growth and shrinkage. If you look at the largest EPC, which is in the control

group and shown here with a red arrow, you see that the point is located below the x-axis, indicating that this EPC decreases in size in the subsequent year. In general, you see that the largest EPCs are shrinking or growing more slowly. This is true for all subgroups, including EPCs in which the mesh has subsided to the group FDA described as lytic.

The scatter plots I just presented suggest that larger EPC grow more slowly, plateau, or even decrease in size. We see this when plotting the average percent change in size shown here.

A literature review suggested that increased risk of vertebral collapse begins when around 50% of the vertebral body is compromised. In our study, the largest EPCs observed out to 5 years occupied less than 8% of the vertebral body with respect to volume, far below the volume predicted by literature to present a risk to vertebral integrity. Importantly, no vertebral body fractures have been reported by sites nor observed by the core lab.

Turning to the qualitative features, the majority of endplate changes exhibited strong signals of stability and healing. The body can compensate for the presence of a void in bone by creating alternative load-bearing pathways in the form of sclerotic margins around bone defects. Therefore, the presence of a sclerotic margin demonstrates healing.

Reactive edema suggests bone turnover and an active biologic process. Therefore, the lack of reactive edema implies stability.

These data show no difference between Barricaid and control groups in the frequency of EPC with these features of stability up to 5 years.

With input from the FDA, Intrinsic developed an EPC stability score to better

estimate and understand EPC progression in the population, as a whole and in the subgroups earlier identified. The stability score combines qualitative and quantitative characteristics into a single measure. The components of the score are EPC growth rate, presence of reactive edema around the EPC, and absence of a sclerotic margin. The scoring scheme ranges from 0 to 7 points, with higher values indicating less stability.

The data shown here are the stability scores for all control EPCs, all Barricaid EPCs, Barricaid with large EPCs, and EPCs with mesh subsidence. As can be seen in each of the Barricaid panels and, in particular, the specific Barricaid subpopulations, the average scores are higher early on. This is an agreement with the FDA's and my own impression that these EPCs appear different than those seen in control when they are first observed postoperatively.

However, in each of these figures, there is a clear trend towards stability over time in each of the EPC subpopulations. By Year 4, these subpopulations were just as stable or even more stable in comparison to control.

We performed similar sensitivity analyses overweighting the different components of the score, and the resulting graphs and conclusions were unchanged.

The stability of EPC over time can be illustrated through examples. I will review two examples of postoperative EPCs that were highlighted in the FDA's Executive Summary, further emphasizing the clinical outcomes of these cases.

This example is of a control patient. The EPC was first observed at Year 1, with no progression in size at Years 2 or 3. At Year 3, a sclerotic margin was identified by the core lab. Additionally, the core lab did not observe any reactive edema. The patient was

reoperated for symptomatic reherniation within the first week postop. No further SSIs were performed, and two other related serious adverse events were reported.

This next example is a Barricaid patient with an EPC with mesh subsidence first observed at Year 2. The size of the EPC reached its maximum at Year 4, and there was no further progression in size at Year 5. Although this was among the largest Barricaid EPCs observed, the patient-reported outcomes were excellent and no reoperations or related SAEs were observed.

As an overview, here is a comparison of the clinical outcomes of all Barricaid and all control patients. The components shown here are associated with the impact of the discectomy procedure. There is no difference between groups. The components on the right side show impact of the Barricaid device: fewer reherniations, fewer reoperations, and fewer related severe adverse events. The stars indicate the statistically significant difference between the groups.

When we restrict the Barricaid group to just those with EPCs, we reach the same conclusion.

In all of the EPC subgroups of interest, we saw the same results. Here, we see Barricaid patients with EPC and mesh subsidence versus all controls. This is the group referred to in the FDA Executive Summary as lytic. The results are similar to each of the other groups: no deterioration of the benefit provided by the discectomy and significant improvement in the critical safety and effectiveness outcomes of reherniations, reoperations, and related SAEs.

The conclusion from this analysis is clear: endplate changes have no effect on the

ability of Barricaid to prevent symptomatic reherniations and decrease the number of secondary surgical interventions, and thus, the benefit provided by Barricaid is maintained over standard of care.

In addition, no significant correlation with EPCs and clinical outcomes were found using other more sophisticated models.

After studying this data, it is my opinion that the Sponsor has captured all qualitative and quantitative features at each time point and has implemented countless analyses and interaction models to understand growth, stability, clinical correlation, and possible predictors, and has done all of these in several subgroups of interest.

In addition to analyses through 24 months, we looked at longer-term data utilizing data from all time points including the post 24-months follow-ups. The benefit and safety that Barricaid provides is observed regardless of EPCs through 5 years.

Here is a Kaplan-Meier survival analysis comparing the rate of reoperations among Barricaid patients with EPC mesh subsidence versus all control patients. The rate of reoperations is substantially lower in this Barricaid subgroup, and the lower rate is sustained through 5 years.

Here is another Kaplan-Meier survival analysis comparing the rate of symptomatic reherniation among Barricaid patients with EPC mesh subsidence versus all control patients. The rate of symptomatic reherniation is also substantially lower in this particular Barricaid subgroup, and the lower rate is sustained through 5 years.

This extensive analysis demonstrates no clinical impact or relevance of EPCs. Instead, they show that endplate changes plateau in size over time. The largest endplate

changes are the same size with or without Barricaid, which is far below the size described in the literature to present a risk for fracture.

Regardless of size, endplate changes in Barricaid patients are not correlated with negative clinical outcomes or any safety issues.

Vertebral body fractures at the index level have not been reported by size nor observed by the radiographic core lab.

Endplate changes have no effect on the prevention of symptomatic reherniation. Thus, the benefit provided by Barricaid is maintained over standard of care.

In my personal experience, I can confirm these findings. While the radiographic images of endplate changes are not desirable, I have not had to perform a single revision surgery nor prescribe any other treatment due to EPCs. Furthermore, in my 8 years of experience with this device, we have not seen a single fracture among the clinical patients.

Thank you. And now I'd like to invite Dr. McGirt to the lectern.

DR. McGIRT: Good morning, my name is Matthew McGirt. I am an outcomes and health services researcher and practicing neurosurgeon in North Carolina. For 15 years I've been studying and publishing on outcomes after discectomy surgery, which is a primary research interest of mine.

The prognosis for secondary and tertiary surgeries in high-risk discectomy patients is not promising. When these patients fail, they often fail very hard. Patients with high probability for reherniation need a device that stops this potentially devastating cascade. Barricaid is the first device supported by Level I evidence that provides a solution to recurrent disc herniation in high-risk patients; it's novel, and I believe it's needed.

Although discectomy is generally successful, a solution for recurrent disc herniation is a challenge that surgeons face every day. Patients who experience recurrent disc herniations are among the most disappointing that I see in my practice. There's clear evidence from multiple publications in the literature that patients with defect sizes 6 mm wide or wider are at an elevated risk for recurrent herniation and reoperation.

I also initially wondered how often a 6-plus millimeter defect really happens after discectomy. I was surprised, when I began studying this phenomenon systematically, that it happens as often as it does. It's not until one begins proactively measuring these annular defects after discectomy surgery do you find that they are often larger than assumed under normal visual assessment. While defect size will vary from patient to patient and surgeon to surgeon, I believe the overall incidence of 6 mm annular defects observed in this RCT is representative.

I can tell you, without a doubt, that the discectomy procedure described in this study is the same as what is seen every day here in the United States. I know this. I've been managing North America's largest registry on discectomy patients for the last 6 to 7 years, consisting of more than 140 hospitals and tens of thousands of patients. My practice group has 32 neurosurgeons, and we conduct over a thousand discectomies each year. I've seen discectomy procedures performed at these sites in Europe under visitation.

Also, with considering the generalizability of patient demographics, surgical techniques, and the study results, this current multicenter RCT with multiple surgeons is far more representative than single-center studies shown to date. For this reason, I believe that the findings of this trial are generalizable to the greater spine practice.

When examining the benefits of the device, Barricaid demonstrating superiority for both co-primary endpoints at 2 years. The Barricaid maintains the pain and functional benefits of standard discectomy while providing three major benefits to patients. Barricaid demonstrated meaningful and statistically significant reductions in symptomatic recurrent disc herniation, also, all types of secondary surgical interventions and all related serious adverse events, compared to their only option now, which is discectomy surgery alone.

So now let's shift gears to the risk side. These include device integrity failures that are defined radiographically and assessed by the independent core lab but that are not necessarily clinically relevant to me or my patients. Most of the observations were not symptomatic or associated with symptomatic reherniations. And actually, only 3% of all Barricaid patients had standalone device integrity observations that were causing or associated with clinical symptoms.

There's also a theoretical risk associated with endplate changes that were observed radiographically but really did not have correlation to clinical outcome. You just heard that these EPCs stabilize and are much smaller than what is reported in the literature and what I would consider to be clinically problematic. These conclusions, including clinical outcomes, all hold regardless of sub-categorization of EPCs, including those that the FDA describes as lytic. For all these reasons, I do not believe that the EPCs will progress or become symptomatic over the longer term.

While these risks are not desirable, associated reoperations are few, and this risk is outweighed by the overall benefit in terms of reduction in symptomatic reherniation and reoperation. This is clearly seen when we look at the data graphically.

The following slides you see here represent all of the studies' available data as failure estimates based on Kaplan-Meier survivorship curves. In this figure here, the y-axis represents the percentage of control patients with a symptomatic reherniation. Patients with large annular defects who only receive discectomy are at a high risk of reherniation with a 25% failure rate at 2 years, 36% at 5 years.

Now, this red circle represents the 2-year rate of reherniations reported in the literature to date, showing that the rates observed in our study are confirmatory of literature to date. But with the Barricaid device, shown in blue here, that risk is reduced. Fewer subjects experienced reherniation compared to control patients. The difference between the two curves is the added benefit of the Barricaid to a discectomy procedure. The greater than 50% reduction at 2 years creates a treatment differential that is maintained throughout 5 years despite few device integrity observations.

A similar story for reoperations. There is a high risk of reoperation for large defect discectomy patients, which is reduced with the Barricaid device, a 50% reduction at 2 years, yielding a substantial benefit that is again maintained throughout the 5-year window.

As a reminder, reoperations are not a single event problem. Secondary surgeries create a cascade of problems for our patients. Patients who are reoperated on never reach the same pain and functional improvement of a patient who did not require a reoperation. The odds of not returning to work were nearly threefold greater when having undergone a revision surgery. Barricaid again demonstrates a 50% reduction in reoperation at 2 years, preventing the chronic disability and improving a patient's quality of life.

And, finally, serious adverse events that are related to either the procedure or the

device: This captures the entire safety profile of the procedure, whether hospitalization or surgery as a result of a reherniation, disc degeneration, endplate change, or anything else related to the device or the procedure. With Barricaid, even though we are adding a device to a procedure that historically otherwise has not had one, the Barricaid cohort experiences fewer related SAEs with a 40% reduction at 2 years and a differential that is again maintained throughout 5 years. Put simply, patients who receive Barricaid have a better safety profile than those who do not.

The Sponsor has provided sound scientific evidence of Barricaid's safety and effectiveness in discectomy patients with large annular defects. In a surgery that typically has great outcomes in this era, recurrent disc herniation continues to be one of the last remaining hurdles in optimizing patient outcome after lumbar disc surgery, and patients with large annular defects are at highest risk. This study, performed in a patient population and with a surgical technique that reflects what I see in my practice, shows clearly that the Barricaid reduces symptomatic reherniation and reoperation and does so safely and effectively.

I personally believe that the benefits far exceed the risk of this easily identified high-risk population, and I'm excited that we, as surgeons, may finally have the first solution proven, with superiority data, to significantly decrease this disabling side effect of recurrent disc herniation after a microdiscectomy.

Thank you for your time today. I'll now invite Glenn Stiegman to the lectern to moderate the Q and A session. Thank you.

DR. RAO: Thank you. I presume that concludes the Sponsor's presentation and

you're here to address the questions that the Panel may have, any preliminary questions?

MR. STIEGMAN: Correct.

DR. RAO: Thank you very much. And thank you for giving us 15 extra minutes. I'm sure a lot of people who have early flights are very happy about that. Well, we can move on now, and I'd like to thank the Sponsor's representatives, all of them, for an outstanding presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? We'll have 15 minutes for this session now, starting from 9:35. Please remember that the Panel may also ask the Sponsor questions during the afternoon Panel deliberation session. The purpose of this 15-minute period is to ask them some brief clarifying questions, some questions where you may want them to come back with data later on in the afternoon. So please feel free to raise your hand and I'll recognize the speaker.

Dr. Sayeed, you had a question?

DR. SAYEED: Thank you, Chairman.

I think it's important just to recognize that Dr. Golish had served on this Panel previously in his role as an advisory member.

So I have a couple of questions. Did the Barricaid device measure disc height? I didn't see that in the presentation. And was there any difference in disc height after placement of the device?

You had also mentioned that you excluded patients due to a lack of conservative treatment and care. What exactly was that exclusion criteria?

And then, you know, finally, in the last presentation, there was a mention of this

question about returning to work and how the Barricaid device prevents secondary reoperation, I'm assuming, by either fusion or secondary discectomy. But does the Barricaid device help people return to work? Is there any data that there is a functional outcome on patients going back to their previous jobs or returning to play or any type of data on true functional outcomes? Thanks.

DR. RAO: Thank you, Dr. Sayeed.

Mr. Stiegman, if you have brief responses, we'll take them now. But this sounds like a question with a lengthier response, so why don't you please make a note of the question and respond to the question in the afternoon session, the purpose being we can get more questions in from more Panel members.

MR. STIEGMAN: Sure. So just to be clear, I heard three questions. One, did Barricaid or did the study measure disc height? And that's a yes, it was actually one of the primary endpoints, so that was -- we can present that result --

DR. RAO: And the return-to-work data we can get in the afternoon. Thank you.

MR. STIEGMAN: Sure. The second question was regarding conservative care and what that means, and those that were excluded due to conservative care, what were those exclusion criteria.

And lastly, do we have any metrics or measurements regarding the Barricaid allowing patients to return to work?

DR. RAO: Dr. Smith.

DR. SMITH: Thank you.

A quick question perhaps to address later. I think it's important to define -- I'm

presuming from your presentation that the decision to return to the OR was at the sole discretion of the operating surgeon, because that function is predominantly into the stated outcome measures and then dismal outcomes to those who had a second surgery. Could you please elaborate later on, were the patients that had a defined symptomatic failure, what percentage of those patients went back to the OR and what were the criteria for the decision to return to OR, if there were any specific criteria?

DR. RAO: Thank you, Dr. Smith. And we'll hold that. Please get us a response to that question in the afternoon.

Dr. Graf had a question, and then I'm going to go to Dr. Finnegan.

DR. GRAF: Carl Graf.

Just one comment and one fundamental question. The first slide that's up is Barricaid is defined as a -- or called an annular closure device. Is it a barricade where you're blocking, or is it a closure device? And maybe you can address that because that might be misleading to some people.

The second pertains back to the question regarding disc space height and how it was measured. Was it on standing x-rays? Was it on supine x-rays? Was it CT? Was it MRI?

And then the third question I wanted to address, that was -- or I wanted to ask, which was partially addressed, was this definition of a box annulotomy. How are we defining a box annulotomy? Because in many cases we're creating, as spine surgeons, a box annulotomy to perform other fusion-type surgeries to make spaces for cages and whatnot, not necessarily for a limited discectomy, as this device has been described its main purpose, intent.

MR. STIEGMAN: Yeah. So if I could ask the Panel Chair to at least address that last point because --

DR. RAO: Sure. Please go ahead.

MR. STIEGMAN: -- I think it is an important detail. So yeah, I think in the FDA's Executive Summary, and you may see it in their presentation -- yeah, we do -- they do call these box annulotomies, and as you described, those have a certain intended purpose. In this particular study, the term "box" is simply a description of geometry of the defect. And so there are three different options the surgeon had: a slit, a cruciate, or a box. So anything that had remotely an opening, those were sort of designated as box because that was the best option.

And so I want to make sure, one, that that's clear; they weren't going in and creating a new box. And, two, if you looked during the presentation, we showed the amount of new created defects versus existing defects and the existing -- the new created box category was low, it was about 26%, and in those results, when we looked at those newly created box outcomes -- in fact, if I could get the new box clinical data. I mean, if you looked at that category, you can see that there's no difference between the two. So we took a heavy presence and looked at that because we knew it was a question of the FDA and it would be a question and discussion topic here, and it really showed no difference.

DR. GRAF: Just one follow-up, Dr. Rao, if I may. One follow-up, because the data presented included the creation of a new annulotomy was actually 39%, it wasn't 20-some percent as you just stated, so I don't know where the difference in the number was. The box annulotomies were noted initially in the control as 57.2%, in the Barricaid at 66.9%.

The created new box annulotomies were actually 39% in the control and 35% in the Barricaid, according to your data that I have here. So that's 39%, which just seems high.

DR. RAO: Thank you, Dr. Graf. If we could just get some clarification on these new box annulotomies, we can do that after lunch.

MR. STIEGMAN: Absolutely.

DR. RAO: Dr. Finnegan.

DR. FINNEGAN: I just wanted to follow up on Dr. Smith's comment. You showed a slide that said one of the controls returned to the OR in 3 days. I think most of us would consider that to be a failure of surgery rather than a failure of the control. So I'm wondering if there's a data point at which you decided it was actually a failure of the discectomy and not a failure of the original index procedure. Does that make sense?

MR. STIEGMAN: Sure, yes. So just to be -- just to make sure I have it documented, the single patient that had an SSI reoperation at 3 days, was that a function of the procedure or a function of --

DR. FINNEGAN: I think most of us would consider that a function of the procedure, and so I'm wondering if there is a timeline. In other words, if they went to, back to the OR within a month, would you consider that to be a failure of the control, or would you consider that to be a failure of the index procedure?

DR. RAO: Dr. Elder, then Ms. Rue, and then Dr. Weisbrode.

Dr. Elder.

DR. ELDER: Ben Elder.

I have a question regarding the patients who went on to require a fusion procedure

as a subsequent surgical intervention. Do you have data on if this was posterolateral or interbody fusions? And particularly for the patients with Barricaid, are there any increased challenges with interbody fusion? And also especially looking at the patients with endplate lesions or changes, if that complicates interbody fusion rates. Later.

MR. STIEGMAN: Sure. Can I address that right now?

DR. RAO: Sure.

MR. STIEGMAN: So, yeah, the short answer is yeah, there was no difference with the procedure, with the complications associated with the procedure. I'd like to call up Dr. Kursumovic to address it directly.

DR. RAO: Let's hold off on that --

MR. STIEGMAN: Sure.

DR. RAO: -- for just a second --

MR. STIEGMAN: I got you.

DR. RAO: -- because there's a lot of panelists with questions. If we have time now in this 15 minutes, the question is really are there complications with interbody type procedures postoperatively, if we have --

MR. STIEGMAN: Right. And the answer is no.

DR. RAO: It was Ms. Rue and then Dr. Weisbrode, Dr. Katz, and then Dr. Wang.

MS. RUE: Karen Rue.

The data you presented, they said the average age was 43, I think, in male, but the criteria included 21 to 75 as to male and female. Is there any data talking about the difference and the endpoint outcomes for the different age ranges at the far ends of the

scale, as well as female and male? Thank you.

MR. STIEGMAN: Yeah, we'll get that after the break.

DR. RAO: If the panelists can keep a note of their questions, because I'm not keeping a note of all the questions.

So Dr. Weisbrode.

DR. WEISBRODE: Steve Weisbrode.

Is there any in vivo imaging data in humans to show a physical relation between the mesh and the endplate changes?

MR. STIEGMAN: Any in vivo imaging to show a relationship between the mesh --

DR. WEISBRODE: Can you see the mesh and can you see any physical relationship between the presence or location of the mesh and your endplate changes?

MR. STIEGMAN: Yes. Well, there is a radiolucent marker at the end of the mesh, so you can see where it goes.

DR. WEISBRODE: And should I be asking, then, is there a correlation between the presence of that appearance and the endplate changes?

MR. STIEGMAN: We'll get you more information after the break regarding that. Thanks.

DR. RAO: Dr. Katz.

DR. KATZ: Lee Katz.

Throughout the presentation there had been references to both MRI and CT, and we've mostly seen CT examples, and I'm wondering, first, in the baboon study, there were MRI images, and it would be great if you could present those. And in the humans, it would

also be important to look at the long term, from surgery out to 5 years for the MR imaging, and I'm wondering if contrast was given in those patients.

My other question: Somewhere it was mentioned that there were birefringent crystals seen at the interface, and I'm wondering if those were further analyzed as to whether they were positive or negative birefringent crystals.

DR. RAO: Thank you, Dr. Katz.

MR. STIEGMAN: So to quickly answer, the contrast, no contrast was given.

DR. KATZ: Okay, but it would be interesting to see the MR imaging as it progressed.

MR. STIEGMAN: Sure.

DR. KATZ: Thank you.

DR. RAO: Dr. Wang.

DR. WANG: Yes. Marjorie Wang.

Along the lines of imaging, I saw that you obtained flexion-extension x-rays throughout the study, and I was wondering if you could provide some data about those.

On Slide 93, if you look at the no reactive edema section, could you make a comment about -- it looks like the Barricaid group has a higher proportion of no reactive edema at Year 2 but lower than control at Year 5, so if you could make a comment about that.

And, finally, do you have any data about the index implantation and perhaps how many times it needed to be revised or if there were endplate violations with that index implantation?

DR. RAO: Thank you, Dr. Wang.

Dr. Subhawong.

DR. SUBHAWONG: Ty Subhawong.

I was wondering if the Sponsor could comment on the location of the endplate changes in relation to the anchor, or specifically, do the endplate changes, are they typically seen on the side where the anchor has been placed or are they on the opposite side?

And then I also wanted to ask -- I think we heard a lot about what the endplate changes do not represent and do not correlate with, but I didn't hear much on the Sponsor's hypotheses as to what they actually represent or what physiologic process could be occurring at the implant and bone interface.

DR. RAO: Dr. Gilbert.

DR. GILBERT: Yeah, Jeremy Gilbert.

Along the same lines, polyethylene terephthalate fibers are known to be reactive inflammatory fibers, and I'm just wondering what work was done to assess the fiber configuration of PET and its inflammatory reactivity.

MR. STIEGMAN: So what assessments were done to look at the fibers, okay.

DR. RAO: Along the lines of the last two questions, you know, I think, is there any correlation between the site of the lesion and the placement of the device? Were the lesions more frequently seen on the base plate side or the mesh side? So I think Dr. Subhawong asked that question.

And along the lines of Dr. Gilbert's question, when you explant the device, which is when I get the sense that most of the histological studies were done, when you explant the device, there's a little bit of tissue attached to the device, and I presume you did the study on that tissue attached to the device. But did you do any study on the endplates

themselves, on the patients who had the explantation done, within the endplates, deep to the endplates, to get some sense of what the histological reaction was?

MR. STIEGMAN: Right. So the answer to that question is no, we did not get any of the endplate tissue. As far as tissues taken during a retrieval, yes, some tissues were taken. It was difficult to tell exactly where that was from, but yeah, we do have tissues and can present that.

DR. RAO: Ms. Starowicz.

MS. STAROWICZ: Yes, this is Sharon Starowicz.

Perhaps a slightly different type of question, more pertaining to the regulatory history, but I would be interested in the Sponsor commenting on why was the decision made to go outside the U.S. to do the clinical trials. It appeared that there was significant interaction with FDA for quite a while before.

MR. STIEGMAN: Sure. Do you want to continue with questions, or can I answer that?

DR. RAO: Just a couple of questions here --

MR. STIEGMAN: Sure, absolutely.

DR. RAO: -- that I had. Let me just go over the questions, and then we'll go to Dr. Donshik for a couple.

My question is really just from the more fundamental level. The device is going into the endplate, and you're recessing it. The sense we get is that the occlusion component is the component that's doing the bulk of the work where it's blocking the annulus. When you're recessing the device into the endplate, what I see on the images available is just the

metallic portion. So how much of the metallic portion is in the annulus? How much of the occlusion component, which is the fiber component, is in the annulus? And how exactly is the device doing the work that it's supposed to do in terms of the mesh component of the device? That's one question.

Number 2 question is, on Slide 97 I saw some posterior ossification, some ossification posterior to the device, and I'm just wondering did you notice this type of ossification on more patients, and is this part of the mechanism? You know, did we get some spontaneous fusions occurring in some of these people?

And if we could have, maybe in the afternoon session, like Dr. Katz said, we've seen a lot of CTs, we've seen a lot of outstanding statistical analysis with lots of bar graphs, and I saw Dr. Gilbert and Dr. Evans just stuck to the presentation where you're talking about the bar graphs. But a lot of us on the table are surgeons, and it would be nice to have some visual longitudinal assessment with both MRIs and CTs, maybe five patients, of how the MRIs change over the course of time in the Barricaid patients and how you're able to assess these patients over time and how the CTs change.

Number 3, more fundamentally, we are seeing that the VAS scores and the VAS leg and the ODI scores are relatively similar in the Barricaid group versus the control group. The question is, if the device is doing what it's supposed to do and blocking reherniations, rather than being similar, should the VAS leg scores and the ODI scores be substantially better in the device group versus the control group?

And, finally, you said that reherniations were blocked in 50.8% of patients undergoing the Barricaid device versus 30% in the control group, but that still means that

49.2% of patients were having reherniations. Now, if the device is doing its work, why are the reherniations occurring? And I'm sure the surgeons who were carrying out the procedures are probably the best people to let us know why reherniations were occurring in those 49.2% of patients. So if you could elaborate on that in the afternoon.

We have maybe 1 minute for Dr. Donshik, and then I want to move to the next thing.

DR. DONSHIK: My question almost follows on or is similar to Dr. Rao. I was looking at the device integrity failure, and there's an overall failure rate of 13%. I did flip through the technique guide that was provided to us, and there were some caveats, obviously, as there are with all surgical implants.

The question is, you know, is there -- and I don't know, maybe you guys didn't stratify this. Is there an increased complication rate, increased device failure rate seen in people who are implanting it for their first through fifth times, surgeons as -- experience driven, I guess, is what I'm trying to say.

DR. RAO: Thank you, Dr. Donshik.

Well, you know, the Sponsors were kind and gave us a little extra time for the questions. If you'd like to respond to some of the questions, we still have some time before 10 o'clock, so please go ahead, Mr. Stiegman.

MR. STIEGMAN: Sure. And I did write down, as quickly as possible, a lot of these questions, but my chicken scratch is inedible. So I think one -- I'll hit some of the --

DR. RAO: I think you mean illegible, not inedible.

MR. STIEGMAN: Illegible, yes.

(Laughter.)

MR. STIEGMAN: So I guess, first, to take Ms. Starowicz's question regarding the IDE, I think that's important because there could be portrayed two different stories if you read both executive summaries. And so the company came to the FDA in 2008 with preclinical testing characterizing the device, as most companies do, as well as a small animal study and I'll just -- I'll put up the regulatory timeline.

Upon review of the device, the FDA requested a baboon study, and that's been discussed briefly and will be discussed more, and the primary outcome or primary objective of this baboon study was to look at really device integrity, toxicity, bone in-growth, whether the device works or not. At the 1-year time point when the baboons are sacrificed, they saw the EPCs, and it generated some safety concerns where the questions were generated.

At the same time, the company had a pilot study of 75 patients in which they had a good handle on safety. They did see EPCs but saw no clinical correlation. During all of this time, they're negotiating the study, the study protocol, with the FDA, so they felt confident moving forward with the randomized controlled study in Europe while the continued discussions around the animal study continued, because they felt comfortable with the protocol after those multiple negotiations.

DR. RAO: Thank you, Mr. Stiegman.

Dr. Finnegan.

DR. FINNEGAN: So I'd like to go back to the basic science because, at least in the materials we have, it's not large information. It's my understanding that this material was used mainly in vascular, and recently, the vascular literature has suggested that if you can use autogenous, it's better than this, although this is better than nothing.

Do you know how much this is in your material, and does it leach out, and did you do serum levels on the patients that you have implanted this in?

MR. STIEGMAN: We'll provide that, try to get that after the break. Thanks.

DR. RAO: Dr. Smith.

DR. SMITH: Thank you.

You presented, in your packet, some very nice preclinical data, and I apologize if this is embedded in there, and it might be helpful just to lay it out. So the device is a mesh that's anchored to an anchor that then goes in something like an open-chain device. And so every time there's a compressive cycle, this device is having some type of force at its interface with the anchor.

Did you show, in your preclinical testing, the total number of stress/strain, you know, cycles to failure, the ultimate strength at failure? And then if these have been implanted in individuals in their 40s, mid-30s, overall design criteria, what's the estimated total number of stress cycles of the life of the implant? And also, if we guesstimate roughly, you know, pressure of a disc, the compressive loads in a disc, and this is the sole anchor point resisting that load, within what level is your design criteria within the levels that it's experiencing clinically? And I'm sure you probably have that data and you can probably extract from what's here, but it would be helpful if you could just outline those points for me.

Thank you.

MR. STIEGMAN: Sure.

DR. RAO: Thank you, Dr. Smith.

I don't see any other Panel questions, Panel members with questions right now. But I think we've given you a fairly long list of issues, Mr. Stiegman, starting with fundamental questions of how the device is supposed to work, why leg pain/ODI were not much better in this group if it's preventing reherniations, return to work status, statistical issues, histological issues, base plate versus mesh-side lesions, were there any correlations, and longitudinal follow-up of imaging studies on a few patients with MRIs and CT scans and the incidence of maybe ossification in the posterior elements from device insertion, and mechanical integrity of the device with biomechanical testing, and the difficulty or ease of repeat surgery with the implantation of the device, and some histological details that Dr. Weisbrode requested.

That was a very good discussion, and thank you to the Sponsor for an outstanding presentation, very detailed, very thorough, and very sequentially and logically presented. I'd like to thank all of the Sponsor's representatives for their presentations.

We'll now take a 15-minute break. Panel members, please remember that you're not to discuss the meeting topic during this break or any subsequent break amongst yourselves or with any member of the audience. We will resume here at exactly 10:15.

(Off the record at 10:00 a.m.)

(On the record at 10:15 a.m.)

DR. RAO: It's now 10:15, and I'd like to call this meeting back to order. Thank you all for taking your seats and for coming back on time. The FDA will now give their presentation.

I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific

request of the Panel Chair.

The FDA will also have 90 minutes to present. FDA, you may now begin your presentation.

DR. HWANG: Good morning, everyone. The following is the FDA's presentation regarding the Intrinsic Therapeutics Barricaid Anular Closure Device that is the topic of this Panel meeting.

These are the current review team for this submission; however, I have left out all the previous reviewers that have provided feedback over this longstanding review of this device. This notably includes Dr. Kimberly Amrami, who was a designated special government employee, to lend her expertise in musculoskeletal radiology in the review of this device.

The purpose of this meeting is to discuss the review of the Barricaid Anular Closure Device. The Agency wishes to obtain feedback from the Panel regarding the study population compared to the proposed indications for use, the study endpoints and study duration, and how to interpret the outcomes measured. Additionally, the Panel will be asked to comment on the significance of endplate lesions and device failures as seen in imaging. Finally, the Panel will be asked to provide a recommendation to the FDA on the benefit-risk profile of the device.

To provide a brief outline, we will be describing the device, a brief overview of the regulatory history. We will then go over some clinical background followed by a study overview. Safety assessments will be presented, which includes evaluations of the findings of the endplate lesions, followed by efficacy assessments, and we will conclude with the Agency's benefit-risk assessments. Key points in the FDA's presentation will be highlighted in blue boxes to help note items that relate to questions that will be asked of the Panel.

First, I'm going to present some basics on the device.

DR. RAO: Mr. Hwang, sorry to interrupt you. For those Panel members who may not be aware, the FDA slides are available on the right-hand side of your folder in print version. Thank you. Sorry.

DR. HWANG: The Barricaid Anular Closure Device is made of three components: the mesh, the anchor, and the radiographic marker located within the mesh. As presented by the Sponsor, the mesh is made of woven layers of PET polymer and is intended to block movement of the disc material out of the intervertebral disc space. The titanium anchor component is used to fix the device to an adjacent superior or inferior vertebral body. The marker component is embedded into the mesh component for the visualization of the mesh.

The Barricaid is offered in three sizes to accommodate various annular defect sizes: 8, 10, and 12 mm widths, with one mesh height of 15 mm. The device is provided with a delivery tool which is preloaded to the device, and other notable instruments include the defect sizing tool and alignment trials.

Please note that the PMA submission included nonclinical and clinical data on all generations of the device; however, the majority of the data was presented on Generation 3 implant and its associated instruments, for which the Sponsor is seeking to market.

There did not appear to be any difference in clinical performance between groups, so data was grouped together in this presentation.

Additionally, the Sponsor is seeking the inclusion of a 12 mm wide implant; however, these were not evaluated in the clinical trial presented.

The Sponsor has proposed the following indications for use, as previously presented. Again, of note: The Barricaid is intended to be implanted following a limited discectomy, to prevent reherniation and recurrence of pain or dysfunction, and intended for patients with large annular defects determined intraoperatively post-discectomy.

Please note that the Panel will be asked to comment on the adequacy of the data provided to support these noted indications for use; however, the Panel may also make suggestions if they feel the data can support a modified or different indication.

Intrinsic Therapeutics submitted an IDE to start a clinical trial in the U.S. The FDA identified safety concerns regarding progressive bone and tissue resorption, described as endplate lesions by the Agency and endplate changes or EPCs by the Sponsor, both reported in animal and early OUS feasibility clinical studies.

The Agency requested a root cause analysis and additional supportive information to address these safety concerns; however, further information was never adequately provided, so an IDE was never approved due to these safety concerns. Subsequently, Intrinsic Therapeutics initiated an outside U.S., or OUS, clinical trial in Europe and communicated their plan to use the OUS data to support initiation of a U.S. clinical study.

There have been many communications between FDA and the Sponsors regarding this product that resulted in various feedback on many different iterations of device, protocol, and study designs.

This is a brief background regarding the preclinical testing presented, most notably the baboon study. Briefly, nine baboons were implanted with the Barricaid device at two levels and a control for discectomy at the third level. Three animals were sacrificed at 3-, 6-, and 12-month time points. The study showed progressive inflammation, which increased over time or at each time point, reaching a severity of 4.8 out of 5. There were observed osteolysis, fibrosis, endplate disruption, and mesh subsidence. There were also reactive changes in response to the mesh component. The size of the lesions continued to grow at each time point and did not appear to stabilize at the last time point.

These images are an example of undecalcified sagittal histologic -- slide on the left -- and the corresponding microradiograph image on the right for the baboon implantation

study at 12 months.

The histologic tissue image is stained with Villanueva's Osteochrome Bone Stain. Note that the purple-stained tissue is the remnant intervertebral disc and cartilage lining the vertebral endplate following the discectomy. The upper device shows superior endplate disruption, as indicated by the white arrow, and mesh, which is the opaque whitish-brown material, subsided into a bone loss or resorption cavity indicated with osteolysis, and green-stained fibrous connective tissue, designated F. The lower device similarly shows both superior and inferior endplate disruption, mesh subsidence inferiorly, and bone resorption cavities with fibrosis.

Next, Dr. John Stinson, the medical officer/reviewer, will present clinical background and study results.

DR. STINSON: Good morning. I'm John Stinson, and I'm a medical officer with the Division of Orthopedic Devices. Before I signed on with FDA after a spinal fellowship in Cleveland, my clinical practice for 25 years was limited almost exclusively to spinal disorders.

Dr. Golish reviewed a lot of this before, but we would like to reinforce that the term "herniated disc" refers to a localized displacement of nucleus, cartilage, fragmented apophyseal bone, or fragmented annular tissue beyond the intervertebral disc space.

Although many definitions exist, the North American Spine Society task force has classified disc herniations into several subtypes, including protrusion, extrusion, and sequestration. The extrusions and sequestrations are most likely to produce leg pain as there is less room for the exiting nerve root. There may be herniation of disc material through the vertebral endplate, as we've heard, into the vertebral body. These are referred to as intravertebral herniations or Schmorl's nodes.

The symptoms of lumbar disc herniation may overlap with those caused by many

other causes: rheumatologic, hip joint, facet joints, sacroiliac joint, or even visceral causes such as kidney stones. So data obtained from the patient's clinical history and physical examination are only moderately accurate in establishing the diagnosis, as there may be many other causes of buttock, thigh, or leg pain.

A patient with a symptomatic disc protrusion will be often asked to fill out a pain diagram, as you see on your upper left. The figure on your upper left shows the dermatomal pain distribution of herniated discs at the L3-4, L4-5, and L5-S1 levels, respectively. We assess muscle, reflex, and sensory deficits that correspond to the nerve root that is compressed. The straight leg raising test for nerve root compression is widely used, and it is typically considered to be positive if pain is reproduced by elevating the leg to between 30 and 70 degrees. These tests are sensitive but nonspecific.

Computed tomography or MRI can confirm a clinical diagnosis of a herniated disk. Imaging is typically only necessary if a patient fails to respond to conservative treatment or if there is a progressive or severe neurologic deficit.

One series of MRI scans on asymptomatic adults showed 27% had a protrusion, 1% had an extrusion, and 38% had an abnormal disc at more than one level, so the herniated discs are found in many asymptomatic individuals. The incidence of new symptomatic herniated discs in the general population has been estimated to be between 1 and 2%.

The natural history of herniated lumbar discs is generally favorable. Most of these will get better within 6 weeks to 3 months.

An MRI or CT scan, as we mentioned, is indicated with patients with persistent sciatica for 6 weeks or more, in whom invasive treatments such as surgery or epidural steroid injections are contemplated.

Elective surgery is an option for patients with congruent clinical and MRI findings and a condition that does not improve within 6 weeks. The major benefit of surgery is relief

of sciatica that is quicker than relief with conservative treatment. Results of early surgical and prolonged conservative treatment tend to even out at about a year so that the patients and physicians should share in decision making.

For patients with refractory sciatic pain and positive sciatic tension signs and imaging evidence of nerve root compression, surgery is an appropriate treatment option. The goal of surgical treatment of a symptomatic lumbar disc is to provide adequate nerve root decompression and minimize soft tissue damage and minimize destabilization.

Disc space access and nerve root decompression may be achieved through a variety of posterior surgical approaches, such as interlaminar or intertransverse approaches.

There is a wide range of surgical techniques that often correlate with a surgeon's training, experience, preference, and local practice patterns. A common surgical approach is microdiscectomy through a small 2 cm incision made after x-ray localization of the involved level. Under magnification, the ligamentum flavum is incised and, if necessary, a laminotomy is performed. The thecal sac and nerve root are mobilized, and the herniation is removed with small rongeurs.

There are both major and minor differences in these techniques. For example, sequestrectomy, when the disc fragment is not in continuity with the disc space, surgeons will often remove the sequestration and leave the annulus undisturbed. To prevent reherniation, some surgeons perform a subtotal or a more aggressive discectomy. The more aggressive discectomy can prevent reherniation, but often can lead to chronic low back pain. The extent of intraoperative decompression is controversial.

Almost half a million lumbar discectomies are performed annually in the United States, and the results are generally favorable with appropriate patient selection. However, outcomes may be adversely affected by a range of factors, including the preoperative duration of symptoms, surgical technique, level of herniation, psychosocial factors, and

pending litigation.

Subsequent surgical interventions in the Spine Outcomes Research Trial: Overall reoperation rates for patients that were surgically treated for lumbar disc herniation was 6% of the cohort by 1 year, 8% within 2 years, 10% within 4 years, and 15% by 8 years, 62 of these patients undergoing reoperation, 62% undergoing reoperation; the reoperation was done because of a recurrent disc herniation and mostly within 2 years of the index procedure.

However, there is a wide variability in reoperation rates among hospitals and surgeons possibly due to uncertainty regarding the indications, practice philosophy, training differences, patient expectations, and local practice patterns.

A recent survey reported that for the first-time recurrent disc herniations, the vast majority of United States spinal surgeons would select the revision microdiscectomy. For a second reherniation, there was a wide variability in the preferences of the U.S. spinal surgeons.

Recurrent lumbar disc herniation: While postoperative MRI can identify the presence of lumbar disc protrusions or extrusions, these imaging findings are very common after surgery and may or may not be related to clinical symptoms.

Assessment of the rates of recurrent disc herniation is challenging due to lack of a standard definition for recurrent disc herniation, the inability for imaging studies to distinguish between symptomatic and asymptomatic reherniation, and because many studies report patients with prevalent pain and do not separate out patients with persistent symptoms from those who experienced initial resolution of symptoms.

One strict definition of recurrent disc herniation considers reherniation as a new herniation occurring at the same level and the same side as a previously operated lumbar disc with a pain-free interval after the primary discectomy of greater than 3 weeks to 6

months. Other definitions require that the return of symptoms be consistent with the previous presentation in the same patient.

As you've seen, on your right is Intrinsic's depiction of the target population, those with large annular defects -- those with large annular defects after discectomy, which the Sponsor has defined as greater than or equal to 6 mm.

Overall, the literature indicates that the reherniation rates after discectomy, overall, range from approximately 3% to 18%. Patients with large annular defects have been reported in literature to have reherniation rates up to approximately 22%, but the range of rates reported in these patients still overlap with those of the general post-discectomy population.

Our understanding of the relationship between intraoperative findings and reherniation rates derives in large part from Carragee's prospective observational study of 180 consecutive lumbar discectomy patients followed from 2 to 6 years after surgery.

Carragee classified disc herniations into four categories:

The first was fragment-fissure herniations. These patients had a small slit-like annular defect through which fragments were removed. Patients with fragment-fissure defects made up almost half of Carragee's patient population. These patients had the best results with only one reherniation.

The second type was fragment-defect herniations. These patients presented with large annular defects allowing removal of the fragments through these defects. They had the highest rate of recurrent herniation at 27.3%.

The third category were patients that Carragee called fragment-contained herniations. These patients had a contained disc herniation and required an oblique annulotomy through which the herniated fragments were removed. These patients had a 9.5% recurrence rate.

The fourth category was the no fragment-contained herniation. These constituted 9% of Carragee's patients. Patients with the no fragment-contained type herniation required an extensive annulotomy for adequate decompression. These patients did poorly. There was a 12.5% reherniation rate, and 38% had recurrent or persistent sciatica.

So the second and fourth groups were at higher risk for reherniation, again, the fragment-defect group presenting with a large annular defect and the no fragment-contained group, which required the surgeon to make a large annular defect for adequate decompression. These are highlighted in blue on the slide because they are the patients most likely to have a large annular defect greater than 6 mm in size following discectomy.

Limitations of the Carragee study included that this was a university referral practice, and the selection of patients for surgery may not be generalizable to all spinal surgery practices, and also there was participation of residents and fellows, and the practice biases of the referring doctors and the attending surgeon may have affected the selection of patients and may have biased the representation of the herniation types in this 180-patient sample. However, the outcomes reported are specific to the Spengler type of limited discectomy where there was no attempt to remove anything more than loose disc fragments.

These additional papers also document recurrence rates in post-discectomy patients with large annular defects. The patients in these series had undergone a variety of discectomy techniques, including limited and subtotal discectomy. In a subset of patients with large annular defects, these papers show a range of symptomatic reherniations. The range was from 2.3% to 22%. In these same studies, the overall post-discectomy reherniation rates ranged from approximately 4% to 14%. While the symptomatic reherniation rate appears to be generally higher in patients with large annular defects, there appears to be overlap in reherniation rates between the large defect group and the

overall post-discectomy population.

As was mentioned earlier with the Miller study, there are several studies which suggest a relationship between annular defect size and reherniation risk. However, it still remains unclear if the annular defect size is the sole or primary factor and how other factors may affect reherniation rate, including the discectomy technique and the extent of the disc resection.

The Barricaid clinical trial began in December 2010, and database lock was this past May 2017. The last subject was enrolled in October 2014.

The clinical trial, as you've heard, was a multicenter, prospective, randomized, largely unblinded, concurrently controlled superiority clinical trial. The study enrolled 554 subjects at 21 clinical sites, all located in northwestern Europe. There were 42 subjects implanted with Generation 2 devices and 225 subjects implanted with Generation 3 devices.

The purpose of the trial was to evaluate the safety and effectiveness of the Barricaid following a limited discectomy compared to the limited discectomy alone in patients at risk for reherniation due to large annular defects.

Key inclusion criteria: Subjects were enrolled with leg pain due to a herniated disc refractory to conservative treatment for at least 6 weeks. Clinical and MRI evidence of nerve root compression was required. However, these criteria permitted inclusion of subjects with either unilateral or bilateral leg pain and did not require that the disc herniation and neural compression identified using MRI correspond to the level and side of the subject's radiculopathy. These factors are subject to interpretation due to nonspecific identification of patients with radiculopathy.

Also, posterior or posterolateral herniations were eligible for study inclusion. Posterior herniations could include a range of locations along the circumference of the disc annulus, for example, central, posterolateral, foraminal, extraforaminal. The surgical access

required for placement of an annular closure device is associated with different levels of complexity and risk depending on location, especially for the treatment of central and extraforaminal disc herniations.

The protocol included no specific definition of radiculopathy nor specific criteria for identification of subjects with radiculopathy.

Also, pathology other than a disc herniation may be responsible for a positive straight leg raising test less than 30 degrees. Additionally, the straight leg raising test used has a degree of imprecision due to the varied angle criteria and its high sensitivity but low specificity for diagnosis of a herniated disc.

The protocol called for the surgeon to measure and record the defect height and width by inserting different-sized defect measurement tools until the tool fits snugly into the annulotomy. Upon completion of the discectomy and measurement of the defect, the patient was randomized, if not excluded due to defect size.

Notable exclusion criteria included osteoporosis, scoliosis, and prior surgery at the index level. The protocol permitted enrollment of subjects with Grade 1 spondylolisthesis and subjects who had undergone prior lumbar surgery not at the index level. These inclusion criteria may have added uncertainty as to the cause of leg pain due to etiologies different from the intended patient population.

This is a schematic of the screening, enrollment, and randomization process. We didn't get any information about the screening process with the PMA, but later, on request, the Sponsor advised us that the patients screened were patients who presented to the clinic with complaints concordant with a herniated lumbar disc. At that point, the investigator was responsible for screening patients per the inclusion/exclusion criteria.

Subjects that passed the preoperative inclusion/exclusion criteria were enrolled in the study and proceeded to surgery. All subjects underwent limited discectomy. The

surgeon then measured the defect size to meet the intraoperative inclusion size criteria. When the size criteria were met, the subject then proceeded to be randomized intraoperatively. Subjects randomized to the control group did not have any additional procedure, while the Barricaid group, of course, received the device.

The protocol called for a Spengler-type limited discectomy alone, with little bone removal and no attempt to remove anything other than loose disc fragments from within the intervertebral space. In the case of a protrusion, an annular incision and removal of all loose disc fragments were performed.

Barricaid patients received the same limited discectomy as the control group and device implantation into either the inferior or superior vertebral body. Successful implantation requires proper alignment, as you've seen, in the sagittal and transverse axes, as well as proper placement above the endplate of the vertebral body. Depending on the location of the annular defect, removal of bone from the lamina may be required to allow adequate access.

These are the key assessments for determination of endpoint success. Patients are screened pre- and postoperatively. In addition to this schedule, during the first year subjects were evaluated at 6 weeks and 3 and 6 months.

Note that MRI and CT scan were performed at screening and then again only at 12 months postoperatively. Without an MRI done shortly after the index procedure, it's not possible to differentiate a true recurrent herniation from persistent herniation where there is missed pathology and a fragment is left behind.

The Sponsor selected two co-primary endpoints. Success for the first co-primary endpoint required a patient to have no evidence of recurrent herniation at the index level at any time up to and including the 24-month follow-up. The purpose of this primary endpoint was to directly measure the Barricaid intended use in prevention of reherniation.

Reherniation was considered as subject failure regardless of whether the reherniation occurred on the same side as the original defect.

Recurrent herniation was confirmed surgically or radiographically, as determined by independent review, unless surgically confirmed that the suspected herniation is not a herniation; for example, scar tissue or residual nucleus material from the index procedure. Reherniations on the contralateral side were included to capture any effect that the device may have on the entire annulus.

To assess reherniation rates, study subjects had postoperative, low-dose, multiplanar CT and MRI at the index level at Months 12 and 24 and were assessed by the core lab using the imaging charter-defined definition for reherniations. Again, the reherniation endpoint was chosen to monitor the device's function.

Given the lack of a generally accepted definition of reherniation, the question is raised: If reherniations contralateral to the index herniation should be counted as device failures, should the device's function be judged by its effect on the original annular defect or on the entire annulus?

The second co-primary endpoint, as you've heard, featured eight components related to pain, function, safety, and radiographic observation, designed to be a composite of safety and effectiveness. Success of each individual subject in the study was determined at the 24-month evaluation time point. The composite endpoint included reherniation success, as discussed previously. The safety component was absence of subsequent surgical interventions at the index level.

There were three components of radiographic success: disc height maintenance of at least 75% of that measured preoperatively, no spontaneous fusion at the index level, and the third component of radiographic success was device integrity.

The device integrity component requires subjects implanted with the Barricaid

device to maintain device condition, which the Sponsor defines as no anchor fracture or occlusion component detachment. The second component was to avoid migration of either the anchor component or the mesh component in order to be a success. Intrinsic graded device condition as intact, fractured, or disassembled. Device migration in the investigational group was graded as anchor-only greater than or equal to 2 mm relative to its initial position, mesh-only, and anchor and mesh both migrated.

The Sponsor selected a minimum 15-point decrease in Oswestry index as a functional endpoint. Functional improvement by VAS leg pain measured the primary pain relief following surgical treatment in both arms. For VAS leg pain, a patient required a minimum 20-point improvement on a 100-point scale for success. The Sponsor cited literature justifying their selection of meaningful clinical differences in measurements in ODI and VAS leg pain.

Intrinsic performed a post hoc analysis of an alternative primary endpoint that assessed clinical performance using what the company considered more clinically relevant endpoints. This alternative composite endpoint considered only symptomatic reherniations, did not consider disc height or spontaneous fusion, and consolidated device integrity under device- or procedure-related serious adverse events. This meant that device integrity failures that did not result in a serious adverse event were not counted towards failure.

As the ODI has a pain component, the Sponsor retained ODI and excluded VAS leg. However, to us, VAS leg appears most relevant in assessing the primary benefit of lumbar disc surgery. Also, ODI primarily addresses low back pain and function, but the questionnaire does not specify the location of pain which is assessed, and the pain may not be attributed to a possible herniation.

The Sponsor did not include the radiographic endpoints of disc height maintenance,

spontaneous fusion, or device integrity. The Sponsor's position is that they do not necessarily predict or reflect clinical outcomes while substantially decreasing the clinical success rate.

However, the radiographic assessments were originally included to assist in monitoring the function of the device. If the device is not functioning as intended, for example, being migrated out of the disc space or disassembled, it is challenging to attribute clinical success to the device.

In addition, there is literature showing an association between loss of disc height after discectomy and longer-term back pain. In the modified composite endpoint, device integrity failures and reherniations were included under device- or procedure-related serious adverse events.

As only symptomatic reherniations have clinical relevance, it appeared reasonable that radiologically diagnosed asymptomatic reherniations be excluded from the analysis. However, the expectation that a functioning annular closure device would prevent both symptomatic and asymptomatic reherniations is also reasonable.

The definition of symptomatic reherniation: We had difficulty with this algorithm. Again, only symptomatic reherniations were adjudicated in the post hoc composite endpoint. The adjudication criteria for identification of symptomatic reherniations were unclear to us, and although we recognize there is no generally accepted definition of a recurrent disc herniation, but this algorithm, there was uncertainty regarding inclusion of symptomatic herniation due to a variety of elements. An unscheduled visit with a radiologic reherniation qualified as a reherniation. Lumbar-related pain is common in a subset of post-discectomy patients, and this method does not assess whether the cause of this pain should be attributed to a recurrent disc herniation.

Also, a neurologic deficit or combined VAS and ODI scores and decreased neurologic

status may or may not accurately determine if a reherniation is symptomatic. Details regarding the criteria used for neurologic assessment were not provided, and the algorithm includes clinical outcomes that may or may not be related to the observed radiographic herniation.

In addition, the algorithm does not consider the possible presence of other painful spinal or extraspinal conditions which may be present.

Lastly, enrollment in the study originally, a physical examination was required for inclusion, and this algorithm does not require a physical examination. So these were the limitations we found regarding this definition, and it had to be considered when reviewing the data.

And as we've explained, these are the protocol-defined and modified study endpoints that have been measured. We look to the Panel for advice on appropriate endpoints for safety and efficacy assessment of the Barricaid device. It would be helpful to hear discussion and understand which of these collected endpoints the Panel may have chosen for their composite assessment to evaluate the device and better interpret the data collected. For example, ideas that we've struggled with are maybe all herniations should be included to assess device efficacy, and symptomatic herniations may be included to assess device safety. Should all herniations be included or just symptomatic herniations? Rather than device- or procedure-related serious adverse events, should we consider all SAEs and device integrity separately? The Panel will be asked, also, to consider appropriate study length.

The Sponsor evaluated these elements through an independent imaging core lab. The imaging charter defined the evaluation of disc height, spontaneous fusion, and device integrity, which were part of the primary defined endpoint, as well as other elements such as disc angle, annular fissures, and Pfirrmann grading. Additionally, the endplate lesions

were measured for area as well as features such as septations and sclerosis.

We will now discuss the patient population and demographics.

The Sponsor states that investigators screened 3,332 patients with symptoms consistent with a herniated lumbar disc and enrolled 647. Screening information was only provided during preparations for the Panel meeting, so no additional information is known. Subjects were enrolled in the study based on inclusion and exclusion criteria, as we discussed. Randomization was performed intraoperatively.

There were 93 enrolled subjects who failed to meet the study protocol requirements during intraoperative screening, mostly for wrong size annular defects, and did not proceed to randomization. Only 26, or 4%, were not randomized because their annular defects were too small. Additionally, some of the other failures were due to inaccessibility; the location was too medial, or the angle was too difficult.

The Panel may wish to consider whether additional revisions or clarifications to the indications for use are needed, including modification of the terms "posterior" or "posterolateral," as use of these terms are vague and may include approaches that are not feasible for this procedure.

This table shows the patient accounting for the study. There was very good follow-up for the study at the proposed 2-year primary endpoint. However, as we discussed before, the Panel will be asked to comment on the appropriate study duration to assess this device. Note that the Agency typically expects 85% follow-up, and the Sponsor was well above that at their 2-year endpoint.

There were no statistical differences between treatment groups in baseline functional outcome scores, comorbidities, or demographics. There are similar baseline data for work status, medication usage, and symptom duration. The overall study included almost 99% Caucasian and 44% current smokers, apparently askew from what we'd expect

in a U.S. population.

Annular defect: We had difficulty reviewing this, reconciling the Carragee types with the expected rates in the Barricaid study. As expected, there were not any fragment-fissure type defects included in the study. As previously mentioned, the patient -- reported not randomizing only 26 patients due to defects being too small, these patients likely being patients that would fall into the fragment-fissure group in the Carragee classification.

However, almost half of the patients in the Carragee study had what he called fragment-fissure defect. There is seemingly a large number of fragment-fissure types that should have been seen in the general disc surgery population. The Sponsor stated that it is possible that many of these fragment-fissure type patients may have been excluded during screening of the 3,000-plus patients who presented to the clinic.

There are also less pronounced differences in the fragment-defect and fragment-contained groups, Groups II and III, in the Barricaid study as compared to the population reported in the Carragee study. It is again important to note that the types highlighted on this slide in blue are the defect types that we would expect to result in a large defect size post-limited discectomy.

In the Carragee series, fragment-contained herniations had been treated with an oblique incision in the annulus and removal of loose fragments, and the reherniation rate was only 9.5%. This again, to us, introduced further uncertainty into the inclusion of patients in this study.

The Panel will be asked a question that includes discussion whether the studied patient population is representative of the U.S. population.

Annular defect assessment intraoperatively: The Sponsor documented the characteristics of the annulotomies performed, including geometry and the resultant defect width and height. From these data, it appears that extensive annular resections were

performed in a number of study subjects, as evidenced by the frequent use of box annulotomies during discectomy. Sixty-two percent of all subjects in this study had box annulotomies. A box annulotomy is inconsistent with our understanding and published technique for limited discectomy, and as was mentioned earlier, has been described in conjunction with a subtotal discectomy and is used during preparation of the inner space for a TLIF or PLIF procedure.

Further on annular defect assessment: Each defect had both height and width measurement. It is unclear how a puncture/slit type of annulotomy, which were performed 28% overall, would have both a width and height measurement. In addition, puncture/slit annulotomies would seemingly not qualify for randomization due to inadequately large defect size. Further, these annulotomy sizes would seemingly be dictated by the physician as the box size or cruciate defect height and width are iatrogenic.

Reviewing a sampling of the operative reports, we did not review all the 554 operative reports; we're reviewing a symmetrical sampling. It is unclear to us how a decision to perform a specific type of annulotomy was made. In addition, intraoperative findings were sometimes inconsistent. For example, one control patient had a fragment defect Carragee type but a fissure annular defect and then a puncture/slit annulotomy.

Another operative reported stated, "We prepared for a Barricaid implant, and the hole in the annulus was 5 on 9 mm. However, after randomization, it turned out that the patient was part of the control group."

We did not review all operative reports, so these are possibly individual cases. However, it raises concerns regarding the investigator's understanding of the study procedures.

We will ask the Panel to discuss the extent of annular resection in the study population and the potential impact on the study.

We will now review safety results in the clinical trial. The safety endpoints for the Barricaid study included adverse events as categorized by the DSMB as serious, device or procedure related, and also device failures and subsequent surgical interventions, subcategorized by FDA as reoperations, revisions, removals, or supplemental fixations. Through previous clinical and preclinical experience, as well as prior FDA feedback, the Sponsor also monitored and provided extensive analysis regarding the endplate lesions.

To show that the Barricaid is safe, the Sponsor collected all adverse event data and had safety data adjudicated independently. All safety data represents the as-treated dataset, so the safety information directly reflects the actual treatment received.

Most adverse event rates were comparable between study populations. Here, we see that there is a clear difference between groups for device-related adverse events, as expected, as the control group received no device.

This table shows 24-month counts of specific procedure- and device-related adverse events germane to benefit-risk determination. Incomplete data beyond 24 months prevents assessment of the probabilities of longer-term specific procedure- and device-related adverse events. The data safety monitoring board shows these, along with GU, ENT, pulmonary, and other categories, as adverse events that showed some notable difference in incidence.

It is important to understand that these adverse events were adjudicated by the DSMB and do not directly correspond to the primary endpoints evaluating reherniation or device integrity.

At 24 months, 19.5% of Barricaid subjects and 1.4% of control subjects had necrosis of bone as adjudicated by the core lab. The osteonecrosis was principally associated with endplate lesions. Periprosthetic tissue was also analyzed from device retrievals that yielded signs of inflammation and necrosis.

This table reviews serious adverse event rates in the Barricaid trial. For any serious adverse event, the control group was 3% higher than the Barricaid.

There were two important measures that resulted in differences in the adverse event rates between the Barricaid and control discectomy cohorts. First, as was noted for any adverse events, the device-related adverse events naturally were driven by the lack of a device in the control group. The device-related adverse events in the Barricaid group were driven by device deficiencies. The control group serious adverse event rate was driven by the number of reherniations.

Index-level secondary surgeries in patients up to 24 months were failures in the primary endpoint. Secondary surgical interventions after 24 months were not counted as primary endpoint failures. This table shows the index-level SSIs cumulatively out to 60 months. The Barricaid group had a lower proportion of subjects with an SSI at all time points. This is due to the increased rate of symptomatic reherniations in the control group that required reoperation.

Note that subsequent surgical interventions continue to occur after the 24-month time point. The incidence of subsequent surgical interventions after 24 months raises the question of the adequacy of the 24-month period for subsequent surgical intervention assessment. However, the long-term data presented should be viewed with caution as there are a number of subjects who have not yet reached the later time points.

By 24 months there were also seven supplemental fixations in the Barricaid cohort and 17 in the control group, mostly due to instability. The Sponsor provided a tabular summary of subsequent surgical intervention events. The information provided was often nonspecific regarding the reason for subsequent surgical intervention. Reasons for SSI in these tables included new/increased pain, discopathy, suspected or confirmed recurrent herniation, and unknown.

Due to the number of subjects that are not yet due at the later time points, survival estimates provide a different approach for analyzing and extrapolating potential long-term performance. On the left of the slide is the survival estimate for the secondary surgical intervention out to 6 years. At 2 years, the group difference in survival estimate is 7% in favor of Barricaid. However, the survival estimates between Barricaid and control groups begin to overlap in the confidence intervals with time.

This table shows reoperations in both treatment groups. A busy slide, we're sorry, but in the Barricaid group, 38 subjects had reoperations at any time through 60 months, and 9 went on to have 11 subsequent reoperations. Reoperations included additional discectomies with and without fusion, fusions, pedicle fixations, wound revisions, decompressions, and Barricaid removals. Thirty-four Barricaid subjects required device removals and/or supplemental fixations with or without discectomy, with or without device removals. The other procedures were primarily performed for wound issues. In the control arm, 57 subjects had reoperations, and 16 went on to have 22 subsequent reoperations. These reoperations included additional discectomies with and without fusion, fusion with pedicle fixations, and others.

There is a higher incidence of segmental fixation/fusion and, of course, device removals among Barricaid compared to control subjects; 34 Barricaid compared to 16 control subjects, respectively, required segmental fixation, fusion, and device removal.

Secondary discectomy and secondary surgery that results in device removal or supplemental fixation are both categorized as SSI failures; however, a secondary discectomy may not represent the same safety risk as device removal and/or supplemental fixation.

We will ask the Panel questions that include discussion regarding appropriate endpoints and how to interpret the data. Please consider additional discussion regarding whether all subsequent surgical interventions should be given equal weight when balancing

a device's benefit-risk profile.

Now, we discussed endplate lesions, and we will continue to do so. Endplate lesions have been an expressed safety concern throughout the review of this device, especially when subsequent surgical intervention involving segmental fixation is contemplated. The concern for these stemmed from observations of the lesions in the preclinical baboon study and previous outside United States feasibility studies.

As of database closure, the Barricaid and control as-treated endplate lesion analysis set included 673 endplate lesions identified by the Sponsor's core lab as existing at one or more time points. These included 483 endplate lesions involved in 235 Barricaid as-treated patients, and that's 88%. And there, 190 endplate lesions observed in 113 control subjects, 39%.

The Sponsor's size analyses show that endplate lesions in the Barricaid group were larger on average and grew faster and appear to show stability at Year 4 or 5. The control group, on the other hand, had smaller lesions on average that did not grow much after initial identification. The control lesions also show more signs of shrinking at later time points. The Sponsor has done exhaustive analyses and has found no clinical implications or effect on outcomes from the presence, location, or size of endplate lesions.

Dr. Amrami will now discuss further qualitative evaluation of endplate lesions.

DR. AMRAMI: Thank you. I'm Dr. Kimberly Amrami. I'm a Professor of Radiology at the Mayo Clinic in Rochester, Minnesota, where I chair the musculoskeletal division, and I hold clinical appointments in both radiology and neurologic surgery.

I was designated a special government employee tasked to participate as a member of this review team given my expertise and 20-year experience as a musculoskeletal radiologist. I have been a part of the review team since previous iterations of submissions over the last 4 years. For this PMA review, I was tasked to perform a qualitative assessment

of a sampling of the imaging related to -- excuse me, imaging provided by the Sponsor. I was tasked with evaluating and qualitatively assessing radiographic findings due to our inability to come to a consensus with the Sponsor's characterization of endplate changes/endplate lesions in the Barricaid and control groups.

I reviewed sets of images for individual subjects from three groups: Barricaid subjects with endplate lesions opposed to the mesh, Barricaid subjects without endplate lesions, and control subjects with and without endplate lesions. Subjects were sampled from each group to represent multiple sites. CT was primarily used, with radiographs and MRIs used to supplement the CT images.

Concern from the review team stemmed from the presentation of all radiographic findings as endplate changes without regard to distinctive radiographic features or observed patterns of radiographic findings. The Sponsor attempted to identify the lesions through core lab assessments of individual features such as sclerotic margins; however, the Sponsor's assessment resulted in different categorization than the Agency. Most notably, Schmorl's nodes are included in all analyses, which conflates the results and does not select for the more concerning lesions related to the device.

I have observed three distinct groupings of radiographic features in the imaging sets provided in this PMA. These groups are endplate changes, endplate lesions or Schmorl's Nodes, and lytic lesions, with an additional subgroup within the latter category where the mesh marker had subsided beyond the vertebral cortex.

Please note that these descriptions in this evaluation are differentiated in this section of the presentation based on the qualitative radiographic assessment. In all other sections, the Sponsor notes all lesions as endplate changes, or EPCs, while the FDA refers to them as endplate lesions, or EPLs.

This slide shows examples of the three types of lesions identified during the

qualitative assessment of the imaging studies in Barricaid and control subjects. From left to right, the images are of endplate changes in a control subject, an endplate lesion at the index level in a Barricaid subject, and a lytic lesion which has developed opposing the mesh in a Barricaid subject.

Endplate changes are generally related to disc degeneration and disc space narrowing. They appear more diffuse and may potentially improve over time. Endplate lesions, a common term for Schmorl's nodes, have a well-defined sclerotic margin that is more discrete and tends to be stable over time. These can often be correlated with disc material seen on MRI. Lytic lesions are typically seen with low density on CT with surrounding sclerotic margins but not present at baseline and are progressive in size.

Endplate changes are commonly seen in all types of disc degeneration/disc space narrowing. In this study, they were most commonly seen in the control group but were present at baseline in some of the Barricaid patients, as would be expected in a group of patients who are candidates for discectomy. The image presented here is from a baseline study of a Barricaid patient.

This set of serial images on this slide is from a control subject. The panel shows the development of endplate changes after discectomy with some changes in the appearance over time, with changes becoming less prominent over time. Progressive disc space narrowing is noted in this case, and a vacuum disc is present postoperatively.

Endplate lesions is an accepted term for Schmorl's nodes. These are common findings in the spine and most often are asymptomatic. Their appearance is characteristic on CT, and MRI can be used to confirm the presence of disc material within the lesion. They are distinctly visually different from the lytic lesions opposing the mesh in the Barricaid subjects. This is a baseline CT for a Barricaid subject. There are multiple Schmorl's nodes present at multiple levels, but not at the index level, in this case.

In this case, there is a Schmorl's node anterior to and unrelated to the mesh end of the device. The MRI confirms the typical appearance at the inferior endplate of L5 with herniated disc material present. No other lesion was present at 12 months at the index level.

Lytic lesions were found only in Barricaid patients and were often associated with the mesh end of the device. This example shows a lytic lesion opposing the mesh at the index level in a Barricaid subject with subsidence of the mesh marker into the lytic lesion, which has enlarged over time. Mesh subsidence beyond the vertebral endplate indicates a breach in the integrity of the cortex, presumably related to either mechanical changes over time from the mesh end of the device, weakening of the endplate due to inflammatory/reactive changes, or some combination of these effects.

The company presented data to say that the percentage of involvement of the vertebral body needed to suggest potential loss of integrity was not reached, but in the case of the lytic lesions and subsidence of the mesh, the cross-sectional area of the vertebral endplate involved in the lytic lesion and location may be more important as a measure than the volume of the lesion as a ratio of the volume of the vertebral body.

Progressive enlargement of a discrete lytic lesion opposing the mesh, small at 24 months but significantly larger at 60 months with mesh subsidence, as seen by the marker position into the lesion. The lesion itself is well defined with a thin sclerotic margin showing that the lesion is slowly growing over time and does not have any aggressive or malignant features.

This is another case in a Barricaid subject showing progressive enlargement of a lytic lesion, which is first seen at 12 months. There is subsidence of the mesh marker seen first at 60 months. Note the vacuum phenomenon within the disc space, which does not extend to the lytic lesion, suggesting that the lesion itself does not contain disc material.

My review of the images led me to categorize the visualized lesions into the three categories discussed in the radiographic portion of the FDA's presentation.

Lytic lesions opposed to the mesh end of the device are visually distinct from both EPL/Schmorl's nodes and endplate changes. From my review of a subset of images, the lytic lesions have been shown to increase over time, and it is not clear that they reach stability in size by 60 months. In many cases, there is a breach of the vertebral cortex opposing the mesh with subsidence of the mesh marker into the lytic lesion. This can also progress over time and is limited by the length of the mesh, so that stability of the degree of subsidence of the mesh marker may not mean stability in the size of the lytic lesion itself. Subsidence may occur as late as 60 months.

The lytic lesions are seen only in the Barricaid subjects, in distinction to the endplate changes and endplate lesions, which are seen in both control and Barricaid subjects. Subsidence of the mesh beyond the cortex of the vertebral endplate indicates a breach in the integrity of the vertebral body. The concern is that these lytic lesions will continue to grow and potentially lead to compression or collapse of the vertebral endplate in this relatively young group of patients.

The Panel will be asked questions this afternoon regarding the safety concerns posed by these endplate lesions and the measures and study lengths that should be performed to assess them.

Next, Dr. Stinson will be continuing with the presentation, discussing the quantitative size analysis of the endplate lesions.

DR. STINSON: Thanks, Dr. Amrami.

Dr. Amrami has described differences between her qualitative assessment of different lesion groupings; however, as previously mentioned, we were unable to reach consensus with the Sponsor how to categorize lytic lesions. Please note that aside from

Dr. Amrami's presentation, all lesions are grouped together and referred to collectively by the Agency as endplate lesions.

However, in quantitative analyses, the Sponsor used subcategories of mesh proximate and mesh proximate with subsidence as potential surrogates for what Dr. Amrami described as lytic lesions and the subgroup about which the Agency has concerns.

The Sponsor developed a method to estimate the size of the endplate lesions seen in this study. They used CT images and found the slice that had the largest area for each lesion in each plane. Using this slice, the lesions were estimated as an ellipse using a major and minor axis. This was done for the sagittal, coronal, and axial planes. Size and growth analyses were conducted per lesion and per subject. Growth rates were examined, and correlations with clinical outcomes were investigated. These correlations were conducted against Barricaid and control groups, as well as numerous subgroups such as subjects with lesions that were mesh proximate or mesh subsided.

This table shows the median endplate lesion size in the overall Barricaid group was larger than in the control group, being 67 mm^2 by Months 48 and 60. This is almost double the control value of 35. Further, the number of occurrences of endplate lesions, while comparable at baseline, was three times larger in the Barricaid group at the primary evaluation time point of 24 months.

Another notable point is the trend observed in the control group areas, which remain relatively stable through all time points. When attention is restricted to the potentially more clinically relevant group of mesh-proximate Barricaid lesions, median lesion area is almost three times larger at 24 months and four times larger at Month 60 in the Barricaid group.

Please note, there are reduced sample sizes at 60 months of 29, 8, and 16 in the

Barricaid, Barricaid mesh proximate, and control groups, respectively, indicating the possible need for more data at this later time point.

Endplate lesion areas were growing notably faster in the Barricaid group compared to the control, particularly at the earliest time point, being 67 mm^2 versus 19 mm^2. There are even faster growth rates in the mesh-proximate group, and the fastest growth rates are found among Barricaid patients with mesh-proximate lesions with subsidence.

However, in all Barricaid groups, the median growth rate is minimal at the last time point of 4 to 5 years. This suggests that the endplate lesions may be self-limiting in size, although there was still some growth in the upper quartiles.

Groupings for mesh proximate and mesh proximate with subsidence was analyzed as a surrogate for lytic lesions, as the Agency and the company were unable to come to agreement on their assessment. In the control group, there are indications that total lesion area is regressing at the last time point with a negative median growth rate of -7.5.

Given the growth of the lesions that do not appear to reach a maximum size until 5 years, we will ask the Panel to consider whether this should impact the time point at which the device should be evaluated.

The Sponsor performed many analyses with subgroups defined by presence or absence of endplate lesions and mesh-proximate endplate lesions, for example, Barricaid with endplate lesions compared to controls without endplate lesions, and Barricaid with mesh-opposed endplate lesions compared to Barricaid with non-mesh-opposed endplate lesions.

There were two notable findings: First, there were lower rates of maintenance of average disc height in Barricaid with mesh-proximate endplate lesions compared to Barricaid with non-mesh-proximate endplate lesions. Second, endplate lesions in the control group were associated with higher rates of symptomatic as compared to

asymptomatic reherniation.

However, given the very large number of comparisons made, it would not be unusual to observe several nominally significant differences purely by chance. Note that the finding with respect to symptomatic reherniation was not replicated in the Barricaid data.

The Sponsor performed analyses of the main effect of treatment, the main effect of lesions, and the interaction of treatment with lesions for various clinical outcomes and an analysis of the correlation between lesions and clinical outcomes within each treatment group. These analyses were also performed in various subgroups, such as patients with mesh-proximate lesions, mesh-proximate lesions with subsidence, large lesions greater than 100 mm, large mesh-proximate lesions, and large mesh-proximate lesions with subsidence.

Note that these analyses and subgroups are post hoc and are based on an outcome variable, in other words, lesions and not a baseline factor, so they should be interpreted with caution.

There were no notable findings and specifically no correlations between lesions and clinical outcomes except for the finding mirroring that described in the previous slide, that there was a correlation between lesions and symptomatic herniations in the control group.

We'll now discuss effectiveness results in the trial. You'll recall that the overall success of the study is based on the Barricaid population achieving statistical superiority over the non-implanted discectomy population for each of two co-primary endpoints independently.

The first co-primary endpoint required a subject to have no radiographic evidence of recurrent herniation at the index level, asymptomatic or symptomatic, at any time up to and including the 24-month follow-up. At 24 months, 50.8% of the Barricaid patients, as compared to 30.1% of the control group, had reherniation success.

Clinically silent MRI-documented disc herniations are common in the general adult

and post-discectomy populations, and as we've noted, the clinical impact of this measured benefit is unclear. However, this endpoint should evaluate the function of the device, which presumably can't distinguish if a herniation is symptomatic or asymptomatic and should prevent all reherniations, which these data confirm. Further uncertainty arises when considering that both rates in the study, both Barricaid and control group, are much higher than that observed in literature, even when comparing asymptomatic reherniations.

For the second co-primary endpoint defined by the protocol, the composite clinical success responder analysis at 24 months, 27.8% of the Barricaid group and 18.1% of the control group were successes, about 10% better for Barricaid. These are the 24-month outcomes of the individual components of the composite clinical success as defined in the protocol. The Barricaid group was almost 20% better than controls in rate of all reherniations. The Barricade group had 7.6% fewer subsequent surgical interventions than the control group at 24 months. Neurologic improvement, ODI, and VAS leg pain successes were comparable, and these benefits, again, they're due to the nerve root decompression and discectomy. Disc height maintenance was 3% better in the Barricaid group.

For the post hoc modified clinical composite success, the Barricaid group had a 12% higher success rate than control, resulting from a 12% higher success rate than control in prevention of symptomatic reherniations and a 7.6% higher success rate in device- or procedure-related serious adverse events.

Both composite endpoints include endpoints that have merit in evaluating this device. The Panel is reminded that there will be questions regarding selecting the appropriate and relevant endpoints. Further, it is important to note that these composite endpoints are based on 24-month evaluation, which may or may not be the appropriate study duration.

Longer-term success for the predefined endpoints: This table shows the longer-term

clinical success in reherniations, subsequent surgical interventions, and device integrity and overall composite success by the protocol definition. VAS leg, ODI, disc height, neurologic outcomes, and spontaneous fusion success rates were comparable.

At first glance, the reherniation and overall success rates appear to converge and appear to reduce to negligible success with time; however, caution is necessary when interpreting these data at later time points. Terminal failures in all patients accumulate, but corresponding transient successes are not counted, and this is a big number at 60 months.

A similar trend is seen in the modified composite endpoint, however not as drastically low. At 60 months, both appear to have success around 50%, though this is out of only 70 patients counted.

The clinical benefit appears to have the potential to lessen over time, and when coupled with the continued growth of endplate lesions with time, it is unclear how the clinical data should be interpreted and whether longer-term assessments should be evaluated.

We again remind the Panel that the endpoints and study length will be a topic in the Panel questions.

Let's look at the individual endpoints, all reherniations. Data shown in this table on the left outlines the number of radiographic herniations observed, resulting in high numbers over time. The table on the right provides the survival estimate that predicts performance, the conclusion being that all subjects appear to continue to develop radiographic herniations if time can progress, regardless of treatment, though the Barricaid group appears to maintain a slowly reducing margin due to a difference in rate in the short term.

Symptomatic reherniations: The results are more similar when considering

symptomatic reherniations. Initially, the rate at Year 1 is 13% better for the Barricaid group but reduces to only a 5% difference by Year 5 when considering known data, shown on the left. When considering a survival estimate, the Barricaid is also 13% better initially and reduces to 9% at 5 years with more significant overlap with the predictive bounds.

Device integrity: Device-related adverse events were almost exclusively in the Barricaid group, as we discussed. Device integrity was assessed using radiographic findings alone and evaluates the device's ability to maintain device condition, that is, no fracture or disassembly and to avoid migration, including mesh rotation, in order to be a success. The Sponsor refers to these two assessments collectively as device integrity.

By 24 months, the core lab reported 32 patients, or 13%, with device integrity failures. Thirteen device integrity failure patients underwent subsequent surgical intervention by 24 months, and 4 underwent SSI after 24 months. Over 60 months, there were 48 device integrity adverse events with data at later time points that are not yet complete.

The primary device failures were mesh detachment and mesh migration. These sequential images show mesh migration through the immediate postop period on your left, 6 months postoperatively in the middle image, and 12 months postoperatively on the right. The marker component is circled, and it's rotated posteriorly.

For mesh detachment, the mesh component physically detaches from the anchor component. For mesh migration, the mesh component rotates posteriorly as determined by location of the embedded marker component on radiographs. In both scenarios, the mesh is no longer sitting in the intervertebral disc space and therefore no longer serving to block nucleus material.

Overall, 22 subjects with device integrity adverse events required reoperations, many of whom had symptomatic reherniations in addition to the device integrity adverse

event. The device integrity failures were clinically silent in many cases and did not necessarily result in a secondary surgical intervention. By 24 months there were successful clinical outcomes in 20 out of 32 subjects with device failure; however, five of these went on to have subsequent surgical intervention after 24 months.

Again, note that relief of symptoms following the index surgical procedure in both groups is due to nerve root decompression, and it is not due to a direct device-mediated effect. It is unclear how to interpret outcomes when the device is not performing as intended and occluding the annular defect. In addition, as device integrity failures continue to present after 24 months, this time frame for outcome assessment appears premature.

Device integrity has been shown to only sometimes lead to negative clinical results or result in secondary surgical interventions. However, while devices with device integrity failures may not immediately require surgical intervention, it may be a matter of time, so utility of this endpoint is another topic of uncertainty. This should be considered during Panel questions and discussion of appropriate endpoints.

The Sponsor collected a total of 63 implant and instrument retrievals during the time frame from the clinical study and commercial use. The Sponsor provided only retrieval analysis on those that were collected from study subjects, and other reasons limited the number of retrievals, such as improper preparation.

A total of 21 retrieval reports were provided in the PMA submission, reporting removal an average of 2.4 years after implantation. These implants were primarily removed due to detachment or migration out of the disc space, new or worsening pain, or instability. It was noted in the reports that 10 out of 25 subjects with revisions only included the mesh, as the surgeons chose to leave the anchor component in if it wasn't loose.

There were similar findings between the failure mode of the Generation 2 and Generation 3 implants despite attempts to strengthen the mesh attachment point. There

were 19 implants out of 21 that showed mesh fraying. Seven of the retrieved implants were due to the mesh migrating into the spinal canal or epidural space or impinging on nerve roots.

Eleven of the 21 retrieved samples had accompanied periprosthetic tissue that was further analyzed using histopathology. From these reports, the Agency found that 9 out of the 11 that included tissue around the mesh showed signs of inflammation. Of these nine that showed signs of inflammation, there was evidence of intracellular birefringent mesh implant particles within multinucleated giant cells and macrophages.

It is important to note that while there is a concern regarding particulate from the device causing inflammation, it may also be concerning if inflammation is caused by physical irritation or the material itself; however, cause of inflammation cannot be confirmed with the analysis, only that it was present.

There were some limitations due to poor description of exactly where the tissue samples came from and the few samples; however, what was seen in the periprosthetic tissue was similar to what was observed in the baboon study.

Whenever histological evaluation of adjacent tissue to the device was done, whether baboon or in clinical experience, there was evidence of inflammation and necrosis. While it is unclear whether the changes in adjacent tissue are due to physical, chemical, or a combination of factors, there are progressive changes that continue to develop over time. It is particularly notable that there is inflammation even at later time points. However, as shown by the Sponsor, there has not been any correlation with negative clinical outcomes from the endpoints evaluated besides the observed failures, which are seemingly comparable to the control group.

The Panel will be asked to discuss their concerns, again, with safety in regards to the endplate lesions.

As discussed previously, the Sponsor designed a clinical trial to power the co-primary endpoints based on 24-month outcomes, and the data, at most, reflect the durability of outcomes through this interval. The benefits of the Barricaid device include the reduction of all reherniations, both symptomatic and asymptomatic. In the Barricaid group, 50.8% were free from reherniation at 24 months. In the control group, only 30.1% were reherniation free, a difference of 20.7% in favor of Barricaid.

The Barricaid device also reduced symptomatic reherniations. In the Barricaid group, 11.2% had symptomatic reherniations at any time through Month 24 compared to double that number, 25.4%, in the control group.

By 24 months, 8.6% of subjects in the Barricaid group received an index-level subsequent surgical intervention compared to 16.2% in the control group, resulting in a 7.6 difference of subsequent surgical interventions in favor of Barricaid.

For reoperations for reherniation, 9% of subjects in the Barricaid group received a secondary operation to treat reherniation compared to 16.9% in the control group, a 7.9% difference in favor of the Barricaid device. Largely because of a higher reherniation rate in the control group, 25% of control subjects experienced serious device- or procedure-related adverse events compared with 17.6 of Barricaid subjects, a 7.5% better performance for Barricaid.

It is important to consider that these benefits discussed are at the 24-month time point. The study duration was based on precedence with previous spinal device studies. However, it may be important to consider the unique progressive changes seen because of implantation of this device.

Subsequent surgical interventions also fall under the risk category. Although Barricaid patients underwent fewer subsequent surgical interventions overall, there is an overall higher incidence of segmental fixation/fusion and, of course, device removals among

Barricaid compared to control subjects, 34 to 16, respectively. These are more complex procedures than a repeat discectomy with potentially a higher complication rate.

Device integrity failure is a risk. At 24 months, 13% of Barricaid subjects had device integrity failures. By Month 24, there were 13 total reoperations of the index level performed at the time or after the identification of the device integrity observation. Two subjects with device integrity failures and successful outcomes at 24 months went on to have subsequent surgical intervention later. After 24 months, the core lab noted 14 instances of migration and 3 instances of device fracture and/or disassembly in 16 subjects. This group required four reoperations for apparent device integrity related adverse events only.

FDA considers endplate lesions as a factor to be considered in assessing the risks of the device. As of database closure, there were endplate lesions in 88% of Barricaid as-treated patients and 39% of control subjects. As discussed, the lesions overall appear distinct between treatment groups in their appearance, size, and natural history. While no clinical outcomes have been associated with endplate lesion subgroup, because of their yet-to-be-determined natural history, FDA considers endplate lesions a risk.

Another risk likely related to endplate lesions is the observed bone necrosis or resorption. At 24 months, 19.5% of Barricaid subjects and 1.4% of control subjects had necrosis of bone as adjudicated by the DSMB.

Other considerations: In reviewing the Barricaid clinical trial, determining benefit-risk for Barricaid, uncertainty resulting from issues related to the study design, the method and type of data collected and analyzed, the observations and results reported, and the absence of patient and investigator blinding were all considered.

The adequacy regarding the characterization of the target population, that is, those with herniated lumbar discs with large annular defects prone to reherniation, were also

considered in the benefit-risk determination. Reherniation rates in patients with large annular defect overlap with those reported in the general discectomy population using a variety of surgical techniques.

There were less patient exclusions based on size of defect than expected, as well as a mismatch of types of defects compared to the literature, which may have been due to inadequate patient selection or investigator training, different surgical standards of practice outside of the United States, or chance.

There is also concern regarding the consistency and technique of discectomy performed, particularly in the control group, as to whether this is an appropriate control group that was studied.

Lack of information regarding decision making and the resultant defect following discectomy introduced more uncertainty in analysis of risk-benefit in the control population.

It is unclear how the selection of endpoints for evaluation should be balanced between clinically meaningful safety outcomes and radiographically observed efficacy outcomes.

The device integrity failures introduce further uncertainty regarding attributing benefits to the device.

Study duration, particularly in light of the progressive nature of the endplate lesions, may need longer-term evaluation to confirm safety.

It is unclear if all benefits are maintained over time, and any initial benefit may need to be weighed against the risk with implanting a device.

Another consideration is the risk of a permanent implant in the generally young patient population requiring lumbar disc surgery. In the Sponsor's series, the mean age was about 42 years. Should subsequent surgical intervention be necessary, the presence of the

Barricaid and/or endplate lesions may complicate revision. Notably, placement of future interbody devices may be difficult or may lead to increased subsidence if endplate lesions are present. Additionally, when considering this younger population, access into the disc as well as intrusion into the endplate may accelerate degenerative disc disease.

Overall, there are many elements introducing significant uncertainty in the evaluation of the benefit-risk profile for this device.

Dr. Hwang will provide brief information regarding a post-approval study and conclude our presentation.

DR. HWANG: I think, in the interest of time, I will sort of skip the post-approval study. Hopefully, the benefit-risk presentation allowed for you to sort of understand sort of our understanding of the data. I just want to bring back points to consider for the Panel, concerns about the study population.

We want you to consider whether the screening process or discectomy procedures conducted led to subjects that are representative of the U.S. patient population; whether the discectomies performed are consistent with the described procedure; whether these reherniation rates in the control population was influenced by the extent of annular resection.

Further, regarding the endplate lesions, whether this data was adequate in determining that the specific radiographic findings are associated with the presence of the device and whether there are safety concerns with device-specific lesions; whether there's appropriate data and whether the appropriate data was measured to evaluate these safety concerns; whether the data presented regarding endplate lesions provided reasonable assurance that the Barricaid device is safe; and whether there are unresolved or long-term safety concerns and, if so, what additional information might be needed.

And, to summarize, the primary composite endpoint included a number of elements.

We would like the Panel to consider, you know, the significance of these device integrity failures; the ability to interpret these positive clinical outcomes regardless of device integrity; inclusion clinical outcomes that are attributable to the discectomy alone; and the utility of measuring all versus symptomatic reherniations.

We would also like comment regarding the study duration and whether perhaps discectomy, fusion, and removal should all be given equal weight in regards to subsequent surgical interventions. We'd just like you guys to consider these points during your discussion and questions for this afternoon.

I guess, thank you for your attention, and we'll take any questions.

DR. RAO: You do have a few minutes if you just want to quickly summarize the post-approval --

DR. HWANG: Sure.

DR. RAO: You have a minute and a half.

DR. HWANG: Okay.

(Laughter.)

DR. HWANG: So the Sponsor proposed two post-approval studies. One is a long-term follow-up, and the other is a new enrollment. It's important to note that while -- sorry, it's important to note that any discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted as FDA suggesting that the device is safe or effective.

The plan to conduct a PAS does not decrease the threshold of evidence required for FDA device approval.

And the premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and efficacy and an appropriate benefit-risk balance.

The Sponsor proposed two post-approval studies, one that follows the OUS RCT subjects out to 5 years to demonstrate if safety and efficacy is maintained, while the other is a new enrolling study that confirms that the Barricaid patient performance is similar to the U.S. population and not inferior to the OUS study.

It is important to note that whenever the use of OUS data is considered, demonstration that this data is representative of U.S. population and that surgical technique is representative of U.S. practice is needed. These differences should be addressed during the premarket review, and applicability should be demonstrated prior to approval.

DR. RAO: Thank you very much. I'd like to thank all of the FDA speakers for their very comprehensive presentations, and I think it's also fair to thank Dr. Stinson for doing the bulk of the heavy hitting for the entire 1½ hours.

Does anyone on the Panel have any brief clarifying questions for the FDA?

Dr. Baron.

DR. BARON: Yeah. And specifically referring to Dr. Stinson's presentation, it seemed there was an implication that Dr. Carragee's study was the standard for the appearance of discectomy for the U.S. population. I find that a little hard to digest given how few patients he had, and that was 2003.

Second, as someone who does hundreds of these procedures, I've never measured my defects, ever. So I can't sit here and tell you what exactly is normal or not regarding this.

(Off microphone response.)

DR. RAO: If you could come up to the microphone. If we could have all the FDA presenters at the microphone, please.

DR. STINSON: -- the Carragee study, but it was the only thing we could really rely on,

and we do recognize it's a university referral practice. There were only 180 patients, and it's one surgeon, and it's a referral practice. But this is the only basis. If you can point us in any other direction, we would be more than interested, but this is the one -- any other papers, this is the one that linked intraoperative findings with recurrence rates, so that's what we had to lean on.

DR. RAO: Dr. Smith. And then Dr. -- and then Sharon Starowicz and then Dr. Gilbert.

DR. SMITH: One quick question. You referenced you reviewed some of the operative reports, and I was wondering if you had a sense to intuitively putting in an 11 and 12 mm one of your devices, almost analogous to putting in a prosthetic cage, in terms of the footprint. Once the patient was randomized to Barricaid, was there any further decompression done, because you, I believe, alluded to the possibility that some of the outcome results may alias the effects of the indirect decompression, mitigating the symptoms of recurrent disc herniation.

Was the decompression done, any other defect measured, and then randomized -- yes or no -- to Barricaid placement, or did some surgeons extend the laminectomy, hemifacetectomy, to deliver some of these devices which are fairly substantial in their footprint?

DR. STINSON: We can't state that with any degree of certainty. We did a randomized sample, and what we saw may have been due to chance. And our problem with reviewing the operative reports is the indications for subsequent surgical intervention were not clear. But we did not document any in our limited sampling of increasing the decompression to fit a Barricaid device in.

DR. RAO: Sharon Starowicz.

MS. STAROWICZ: Yes, this is Sharon Starowicz.

I have a question, Dr. Stinson, hopefully you could clarify. I think, in the survival

analyses, you were providing a particular approach for that analysis and cross-sectional approach and it is -- and again, I'm not a statistician, but I think you --

DR. STINSON: Neither am I.

MS. STAROWICZ: I think you had caveated it with the fact that this particular type of analysis may, in fact, bias more toward failure, that failures are counted in the analysis regardless of the time period that they occurred, but yet successes aren't measured until the patient is actually in or due for that particular visit. So I was just curious if you could comment on it because my understanding was that this particular survival analysis technique is not the one that FDA recommends in their guidance for spinal devices.

DR. HWANG: I guess, which technique were you talking about? So they presented both, or I guess we presented both basically, the data that exists and then the survival analysis, which the Sponsor referenced that this was part of FDA guidance. It was a general FDA and general -- I'm not sure that the CDRH actually was a part of that one, but it does provide sort of an estimation of the information that we have and how it might be -- how it might proceed in the future given, sort of, limited future data. So I don't want to say that it's -- or we think that it's an appropriate way to present the data that we have, if that makes sense.

DR. RAO: Thank you.

Dr. Gilbert, please.

DR. GILBERT: Yeah, Jeremy Gilbert.

A couple of things came to mind in looking at this presentation. First, in the analysis of the lesions and the CT scans, particularly Slide 58, it's apparent to me that the titanium nub that holds the fiber mesh sits proud into the disc space and looks like, in fact, it contacts the opposing vertebral body rim and induces some additional bone formation there and a point contact of loading between the device and the opposing vertebral body.

I'm wondering if that's just this slide or is that a common appearance. In other words, is there sort of a heterotopic or hypertrophic formation of bone that arises because of that titanium contacting the rim, and is that at all associated with the development of these lesions?

In particular, and let me just link it, if there is this pinching or point contact between the two, there's fiber between those two parts, which we call fraying, but to me it may be sort of this contact stress disruption or fracture of the fibers that leads to formation of the debris. So I'm trying to understand that biomechanical element of potential interaction of the implant with the lytic lesions.

DR. AMRAMI: I can't really speak to the biomedical part of that question, but I would say that it's very variable. The appearance of that sort of, I guess what I would call the neck of the device, the part that connects the anchor to the mesh, it doesn't always contact that way. Sometimes there are lytic lesions associated with the mesh -- excuse me, with the anchor, but they're always associated with the primary part of the anchor that seems to be very well integrated into the bone in most cases. And those cases that have the small lytic lesions associated with the larger part of the anchor actually did not really seem to change very much over time. I understand what you're saying, based on this case, that observation, that that could potentially be an issue, but that's not my observation and what I reviewed.

DR. GILBERT: Thank you.

DR. RAO: Thank you.

Dr. Katz, please, and then Dr. Subhawong and then Dr. Elder.

DR. KATZ: Lee Katz.

I actually also have a follow-up for Dr. Amrami. Aside from the one example you gave, in your review, did you find other cases where there was progression of the endplate

lesions, as you demonstrated here in this slide? And at the same time, again, I'm going to ask about MRI. I don't know if there were MRI cases that correlated with this and what were those findings.

DR. AMRAMI: Definitely, there were other cases that had progression of the endplate lesions, particularly in the control group, so the answer to that is yes. I did not use the MRIs as the primary evaluation I was doing. I was involved in reviewing the baboon images as well, and it became very clear that there were these lesions associated with the mesh, and that was the focus of my review. So I did use the MRIs sort of as a secondary check if there was something that I was thinking might be a Schmorl's node, but I wouldn't say that I used that as my primary evaluation. And I did not do any kind of evaluation for the primary herniation or reherniation of the disc.

DR. KATZ: What about in other of the Barricaid patients? You said there was progression in the control group, but were there other patients in the Barricaid group that also demonstrated the progression in your review?

DR. AMRAMI: With which type of finding?

DR. KATZ: In CT, using the CT.

DR. AMRAMI: So, definitely, the lytic lesions progress over time.

DR. KATZ: Yeah.

DR. AMRAMI: The endplate changes, again, probably show the similar pattern to the control examples. The control examples, I would say that they tend -- the endplate changes seem to be more obvious than in the Barricaid patients over time, but definitely they did have some similar changes.

DR. KATZ: Thank you.

DR. RAO: Dr. Amrami, just while you're there, on a similar vein, was your task restricted just to the assessment of the endplate changes, or did you simultaneously look at

the MRIs and assess whether -- how reherniations were assessed or diagnosed? The ability to diagnose a reherniation on an MRI scan when there's an implant that's close by, did you look at any other aspects of the data, or was it just restricted to endplate changes?

DR. AMRAMI: I was tasked with evaluating the endplate lesions, and again, that came out of some of the earlier evaluations of images in humans and in the animal study. So, no, I did not review for reherniation or anything to assess the primary diagnosis.

DR. RAO: Okay. Well, hopefully when the Sponsor presents that data after lunch, we'll be able to look at the MRIs and see --

DR. AMRAMI: Um-hum.

DR. RAO: -- what's the assessment.

Dr. Stinson, do you have any thoughts on assessment of MRIs for reherniation in the presence of an implant?

DR. STINSON: When we first looked at the Sponsor's algorithm for reherniation, we saw and gave them credit, they put a lot of thought into it; however, there was still -- if you took it further apart, there was still a lot of uncertainty and the possibility for inclusion of patients with symptoms not related to the reherniation. The biggest problem we had with the reherniation algorithm was that there was no physical examination required to be diagnosed as a reherniation, while that was a very strict part of the inclusion criteria.

DR. RAO: Sorry, Dr. Subhawong.

Just to follow up on that, I wasn't 100 percent clear. What were the criteria for diagnosis of a reherniation? Was the MRI done strictly on protocol at 12 months, 24 months, or was an MRI used to diagnosis a reherniation?

DR. STINSON: If a patient had new symptoms, then a new MRI was performed. However --

DR. RAO: So MRIs were obtained to diagnose --

DR. STINSON: MRIs were obtained.

DR. RAO: -- every reherniation?

DR. STINSON: Yes, there was a radiologic confirmation of the reherniation.

DR. RAO: You had something to say?

DR. HWANG: No. I guess I just want to be clear. Do you mean all reherniations that's the primary, part of the primary -- previously established primary endpoint, or are you talking about the symptomatic?

DR. RAO: Either one. Was an MRI obtained to diagnose a reherniation?

DR. HWANG: Yes.

DR. RAO: For every reherniation an MRI was obtained?

DR. HWANG: I believe so.

DR. RAO: Thank you very much.

Dr. Subhawong.

DR. SUBHAWONG: It's Ty Subhawong.

The question is for Dr. Amrami. I understand you may have only had access to a subset of the imaging, but I was interested as to whether you were able to go back to correlate the imaging findings with the specimens or with the implants that had been retrieved. Did the Sponsor provide that data to you, and you know, my question would be were there any imaging findings which might have predicted, you know, failure to implant in the ones that were retrieved?

DR. AMRAMI: No, I did not have access to that, and I did not specifically review for that finding.

DR. RAO: Thank you.

Dr. Elder.

DR. ELDER: Yeah, Ben Elder.

To go back to some of the discussion about conducting a trial outside of the U.S. versus the original IDE submission, Dr. Stinson identified several issues and questions for us regarding inclusion/exclusion criteria, definitions for recurrent disc herniation, as well as components and then composite endpoint. Were these discussed after the initial IDE submission identified prior to initiation of the outside U.S. study?

DR. HWANG: So are you talking about -- so for identifying the symptomatic?

DR. ELDER: Right, I think some of the concerns that have been addressed during your presentation.

DR. HWANG: So the Sponsor developed those with, I guess, the DSMB. So there's been discussion on a lot of different things. We've provided input on different parts of it. Specifically regarding how to determine symptomatic, I don't believe so, but we can go back and check.

DR. RAO: You can come back to that.

DR. HWANG: Yeah.

DR. RAO: Come back on that.

Just one second, Dr. Sayeed. Dr. Kim hasn't said anything, so I'm going to give you an opportunity to ask a question.

DR. KIM: This is Dr. Bong-Soo Kim from Temple.

Do you have any data or information on the relationship between subsequent lumbar fusion and endplate lesions?

DR. HWANG: I'm sorry, subsequent --

DR. KIM: Lumbar fusion procedure and then endplate lesions.

DR. HWANG: So what was completed --

DR. KIM: Any relationship and you see any data.

DR. HWANG: I guess we would have to go back and look, but --

DR. RAO: It goes back to Dr. Elder's question, and I think we're waiting for the Sponsor and maybe the FDA also to give us any information you have on the relationship of device placement versus ease of subsequent operations.

Dr. Sayeed, you had a quick question. We're running out of time, so just keep that in mind.

DR. SAYEED: Sure.

DR. RAO: Yeah.

DR. SAYEED: You know, if there's a suspicion of the mesh, you know, forming this inflammatory response leading to these lytic lesions, in the cases where you had the device migration, were there any -- was there any enhancement in MRI in cord or nerve root?

(Off microphone response.)

DR. RAO: I think she said didn't personally evaluate that.

Dr. Finnegan.

DR. FINNEGAN: A question for Dr. Stinson. If I do orthopedic math and there were 21 sites, that means there were about 26 patients per site, which is 13 plus 13, but we heard that somebody did 40 Barricaids, which I would assume they also did 40 controls. So do we have any idea about the numbers per site? In other words, did several sites only do one or two, and then what is the relationship of their results to the end results?

DR. HWANG: Either us or the Sponsor can get back to you on that.

DR. STINSON: Yeah.

DR. RAO: Thank you.

DR. STINSON: We have data on that, and the distribution was fairly even, but we can get back to you on that. There was a learning curve analysis that the Sponsor also did as well. We can get back to you on the details.

DR. RAO: Dr. Weisbrode.

DR. WEISBRODE: I guess I did have some concerns --

DR. RAO: Turn your microphone on, please.

DR. WEISBRODE: Thank you. Sorry, Steve Weisbrode.

I had a concern over the use of the word "progressive inflammation" used to describe the baboon, the endplate lesions. The data to identify inflammation are inconsistent and at times not available, as indicated by the study pathologist that indicated "due to artifacts." And so I just have a concern over this, especially a lead-off statement that there was progressive inflammation. Fibrosis, yes, but identified cellular inflammation in a consistent level was not.

DR. HWANG: I guess we do have a backup slide on that. Oh, we didn't send -- okay, we can show you a slide on that later.

DR. RAO: Okay, thank you.

Any other questions from the Panel for the FDA?

Dr. Sayeed.

DR. SAYEED: Just in terms of -- I guess it's Slide 43, in terms of, you know, disc reherniation rate, there's a difference of -13.8% versus bone necrosis of about 18%, unfavorable to the device. Is the FDA's conclusion that there's more adverse events with the device compared to -- you know, obviously, bone necrosis doesn't qualify for a secondary surgical intervention, but in terms of adverse events.

DR. HWANG: So I guess it is important to note that these were just the ones adjudicated by the DSMB. So the sort of -- you know, whether all of the lesions were captured under this or whether it was true necrosis or resorption, it's sort of just as adjudicated by the group. So I think that the implications of it are a little bit more limited.

DR. RAO: Thank you, Mr. Hwang.

We will now break for lunch. It's 12:02. Panel members, please do not discuss the

meeting topic during lunch amongst yourselves or with any other member of the audience. We will reconvene in this room exactly at 1:00, and any Panel members who have questions are free to ask at that time. We should have a fair amount of time to carry out the discussion. I will ask that all Panel members please return on time. Please take any personal belongings with you at this time. The room will be secured by the FDA staff during the lunch break. You will not be allowed back into the room until we reconvene. Thank you. See you at 1:00.

(Whereupon, at 12:03 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. RAO: We're back at full strength. It is now 1:01, and I would like to resume this Panel meeting. We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Commander Anderson will now read the Open Public Hearing disclosure process statement.

CDR ANDERSON: Good afternoon.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of the meeting. For example, this financial information may include a company or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you.

DR. RAO: Thank you. For the record, we have received one request to speak for today's meeting. Each speaker will be given 5 minutes to address the Panel. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate

transcription of the proceedings of this meeting. The Panel appreciates that each speaker remain cognizant of their speaking time.

The first speaker is Danielle Shapiro. Is Ms. Shapiro here? A Ph.D. She is Senior Fellow at the National Center for Health Research.

Dr. Shapiro.

DR. SHAPIRO: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Shapiro. I am a doctor and senior fellow. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policymakers. Those are the perspectives that I bring with me today. We do not accept funding from device companies or industry, and I have no conflicts of interest.

Three to five percent of the U.S. are affected by lumbosacral radiculopathy, and the vast majority can be managed conservatively. If indicated, simple discectomy is the most common surgical treatment option; however, it is unclear if it prevents back or leg pain from persisting or returning beyond 2 years postop.

The Barricaid device is first of its kind, but since the surgery itself has unclear benefits, the device should only be approved if it adds a proven, meaningful benefit for patients. True, there is evidence of benefit at 24 months postop; however, the trial failed to demonstrate benefits in the long run and raised many concerns of potential harm. Patients deserve better evidence. We have several major concerns.

Number 1: If approved, Barricaid would be indicated for annular closure following limited discectomy; yet, in the study, 62% of those surgeries included annulotomies, or carving out of the annulus, which is a more extensive surgery. In other words, the proposed indication does not match up with the surgery for which the device was tested. This raises important questions:

1. How effective is this device at closing natural annular defects without annulotomy? And
2. Was annulotomy responsible for the increased reherniation rate seen in both Barricaid and control subjects?

Number 2: The long-term performance data does not indicate effectiveness. It is worrisome that the device had superior outcomes at 24 months postop but not after that, because we already know that the benefits of surgery decrease after 2 years. Patients need a way to prevent back pain and symptoms from coming back or a way to at least postpone a second surgery. The long-term data do not demonstrate that the device will meet either of these needs.

The FDA's analysis indicates that 50% of Barricaid subjects had reherniation compared to 70% control; however, this 20% advantage of Barricaid over surgery alone drops down to a non-significant 6% in the long run. In addition, although there was a decrease in second surgeries in Barricaid during the first 24 months, there were numerous second surgeries after 24 months that should be counted as failures, and Barricaid patients had more second surgeries that required implanting hardware and fixation, which is a higher-risk procedure. The FDA should require the Sponsor to demonstrate benefit beyond the initial 24 months before approving this device.

Number 3: We have concerns that this device will do more harm than good. There were substantial device integrity failures, including device fracture and migration. The Sponsor asserts that these mostly still had positive clinical incomes; however, that raises a question about the value of this device. If the device fails but the patient does well, does that suggest that it's the surgery that is providing benefit and not the device? We're especially concerned that Barricaid patients had nearly twice the percentage of endplate lesions and these lesions had more worrisome features with bone erosions likely caused by

the implant. The data also suggests that EPLs contribute to reherniations. Bone erosion can cause serious harm, such as elevating blood calcium levels, increasing inflammation, or disrupting normal homeostasis of bone buildup and breakdown. And could these cause bone fracture or even bone cancer? We need 5-year data to address these potential risks before approving this device.

Number 4: The lack of blinding raises questions about the integrity of the data. If primary endpoints are based on findings seen on x-ray, then not blinding subjects is not of concern; however, composite assessments include patient reports, and that could be high risk for bias. If we can't blind outside the U.S., the FDA should require blind studies within the U.S. to minimize the risk of bias.

Number 5: Our last concern is that there are no data on the 12 mm size device, and without that, we should not consider that size for approval.

In conclusion, patients who suffer with back pain need better alternatives for long-term relief. This device might be the answer, but limited data provided suggest it's unlikely to offer the kinds of benefits that patients need. The study indicates substantial device failures. Its use in limited discectomy remains unknown because most patients had the more extensive surgeries. In addition, short-term benefits appear to be modest and wane after 24 months or 2 years.

Long-term studies with blinding conducted in the U.S. can provide more certainty, but at this time data are insufficient to recommend approval. We respectfully urge you to vote no on this device as the data do not prove that the benefits outweigh the risk or provide a reasonable assurance of safety or effectiveness.

Thank you so much for the opportunity to share my organization's perspective. Thank you.

DR. RAO: Thank you, Dr. Shapiro.

Does anyone in the audience wish to address the Panel at this time? If so, could you please come forward to the podium and state your name, affiliation, and state your financial interest? You will be given 3 minutes to address the Panel.

(No response.)

DR. RAO: Since there are no speakers, we're going to move forward. Are there any questions for the open public speakers?

(No response.)

DR. RAO: I now pronounce the Open Public Hearing to be officially closed. That gives us a lot of time for the Panel deliberations. We will now continue the Panel deliberations. As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

This is now a good time to have the Sponsors and the FDA respond to the questions that were asked of them this morning. Traditionally, the Sponsor goes first. If the Sponsor doesn't have any objections, I'm going to have the FDA go first because their questions were shorter, and some of them, some of the questions that were asked of them were actually -- I think they're going to refer back to you. So does the Sponsor have any objections if we go first with the FDA response to the questions?

(No audible response.)

DR. RAO: So seeing that there's no objections, I'm going to ask David Hwang from the FDA to move forward with responding to the questions that were asked of the FDA this morning.

DR. HWANG: Okay, so I think most of our responses are a little bit of a clarification. In regards to Dr. Baron's comment regarding Dr. Carragee's study, I think we tried to

acknowledge that there are limitations for just using the one. The initial reason why that one was focused on was it was part of the IDE study in which they sort of presented it, at first, so that was sort of the basis of where we're coming from.

In regards to Dr. Smith's question about whether any additional procedures were done for Barricaid to make sure that it was sort of as implicated by some of the op reports, I think we want to note that, you know, sort of the op reports are very inconsistent and lack some of the detail that we would've liked. I think that some of that might've been lost due to translation from what was, sort of, transcribed.

Let's see. To Dr. Gilbert's question regarding, sort of, contact for the titanium endplate -- or sorry, titanium portion of the device, as Dr. Amrami noted, it was sort of inconsistent where it wound up, and I think that that's some of our lack of understanding of what is sort of an appropriate place that it's supposed to wind up. I think, sort of, the patient imaging sort of shows all of the kind of varied differences.

In regards to Dr. Katz's question about using MRIs and radiographs, I think Dr. Amrami just wanted a clarification that it was -- CT was focused on and that a lot of the MR and radiograph image quality was a lot more consistent.

Dr. Rao's question in regards to whether the MRIs were re-reviewed sort of in terms of how to measure reherniation, we didn't specific look at -- specifically re-analyze how the reherniations were measured. In terms of reherniation, I think that we didn't particularly suspect that there was -- it would be a difficulty, as I think there is a number of literature that does show that, you know, asymptomatic imaging only can be observed, so we didn't specifically look at that again.

In regards to Dr. Elder's question about some of the endplates -- I mean, sorry, endpoints and whether we previously commented on what the study endpoints would be, again, there was a lot of discussion on a lot of the points. We specifically did not comment

on how to measure symptomatic reherniations, but again, things have changed a lot over time, and there were many, sort of, rounds of discussion.

I guess Dr. Kim and Dr. Elder's comment about the difficulty of surgery and specifically what types of surgery followed, the Sponsor will sort of follow up a little bit more, but I do want to note that most of their difficulty analysis came from time and blood loss and things like that.

And then I guess Dr. Sayeed had a question about whether some of the migrations impinged on nerve roots. I think there were some, it wasn't all, so it wasn't necessarily if it migrated; it definitely did that, and again, like Dr. Stinson noted, at later time points. Sometimes they weren't initially -- there wasn't initially a problem noted, but then later on it required surgery, so sort of a mixed bag.

And the Sponsor -- in regards to Dr. Finnegan's question about the Sponsor's -- the study sites, the Sponsor will address that.

And, lastly, Dr. Weisbrode's question about progressive inflammation, I guess we have some backup slides that Dr. Mog will cover.

DR. MOG: I'm Steven Mog. I'm a veterinary pathologist with the FDA. So I just want to answer the question about the progressive inflammation and progressive fibrosis.

Okay, this slide shows an overview of what we saw in the baboon study as far as adverse lesions. So we have six adverse lesions. They did a discectomy at L3-L4. Well, let me first start by saying a baboon has seven lumbar vertebrae, so humans have five. So the L3-L4 is a control discectomy level. Then there were two devices, one at L4 to L5 and one at L5 to L6. And we have three time points: 3 month, 6 month, 12 month. The particular information which we summarize as inflammation around the mesh progressing from 1.7 at 3 months to 3.3 at 6 months to 4.8 at 12 months comes from the appendix, summary appendix, and if you look at PDF page 71, you can see the individual animal data. For

example, for the 4.8 there were three animals that had Grade 5, two animals that had -- at L4-L5, and then L5-L6, there were two animals with Grade 5 and one with Grade 4. That's how we came up with the overall score, which Alizée Pathology reported, so we're just summarizing their results. In addition, we put osteolysis, we added osteolysis, tabulated that, because that was in the narrative of the report but not tabulated in their appendix. So all the data is in the Executive Summary appendix.

DR. HWANG: Were there any other follow-up questions or --

DR. RAO: Is that satisfactory, Dr. Weisbrode?

DR. WEISBRODE: Steve Weisbrode.

I see these numbers, and I went over the appendices and saw how those were generated, but from the histologic slides and from the statement made by the study pathologist, it wasn't possible to recognize histologic evidence of individual cells, so with some staining for some markers, it would be reflected. But I think the consistency of those observations were not impressive to me about being able to make statements about the degree or the types of inflammation. I thought we would be very limited from the slides that we were able to see. And it had to do with -- as the study pathologist said, it was the inability to get the methyl methacrylate to penetrate adequately through the specimens. And as I looked at the images of the slides, it did seem like it was the device, the mesh of the device may have physically impaired some of the penetration of that plastic because it looked like the images on the control slides were a little bit better.

DR. MOG: If I can respond. You're absolutely right. The thickness of the slides, because they're ground, un-decalcified slides, they were 120 microns. It's very difficult at 120 microns to get any cellular detail. However, the study pathologist said, based on her evaluation, that she called this inflammation and categorized it that way, so we accepted that. And I think you can also see, in other cases, where we have thinner sections that use

paraffin that are inflammatory cells in other instances. So I appreciate that comment, but we went with what was in the study pathology report.

DR. RAO: Dr. Gilbert, any thoughts on the histology, based on your background?

DR. GILBERT: Jeremy Gilbert.

So my comments on this have to do with the Dacron fibers themselves, that there is literature out there that describes inflammatory reactions to Dacron fibers. You simply have to go to Google Scholar and type in Dacron fibers and inflammation, and you'll find several of those articles, and one, in particular, actually utilizes Dacron fibers to induce inflammation for a specific medical effect. And so Dacron fibers, PET, are known to be stimulatory to inflammation. You don't need particles, per se, for that to occur, as has been demonstrated in literature. So I'm just wondering at the choice of Dacron as a material for this particular application.

DR. MOG: May I show three slides on that issue? This is the summary of the retrieval or the periprosthetic histopathology that we reviewed, and we looked at the initial seven explants and an additional four explants that were submitted to the FDA. Out of those 11, 7 had particles and 9 had inflammation, so that was presented earlier. This is the summary of that showing inflammation in nine, and of those, seven had particles. There were two that had no inflammation, no particles, based on our evaluation.

And two examples of the inflammation that's seen with those mesh fibers that are birefringent, anisotropic. I know the image is kind of small, but the large white particles, this is actually an H&E slide with polarized microscopy, and the arrows point to giant cells, the double arrows, and the smaller arrows in the lower left show actual fragments of those mesh fibers in multinucleated giant cells. And here is one other picture of that, if you want to see the larger giant cells. So we do see a response to the mesh particles, the mesh fibers, in at least a subset of explants.

DR. RAO: Dr. Weisbrode.

DR. WEISBRODE: I'm sorry, I just wanted to clarify that I don't have any doubts that inflammatory cells are present in the lesion. I would expect them to be as documented by these kind of observations. I just don't think they were well documented because of the artifacts --

DR. RAO: Any other questions for the FDA on their responses to our earlier questions?

(No response.)

DR. RAO: Okay, so let's move forward. We'll move ahead with the Sponsor's response to our questions. And if I may ask, could we go to the basis of the implant? How is the implant supposed to be working if we recess the hub of the implant and if the mesh part is inside the disc space? How is it supposed to be restricting recurrent herniation? Number one.

And number two, if it is restricting recurrent herniation, should we expect the incidence of leg pain to be dramatically less in that group of patients?

MR. STIEGMAN: Sure. So that was actually where I was going to start as well. I'd like to call up Dr. Kursumovic to discuss sort of the fundamental design and the chance of reherniation, and then I'm going to bring up Dr. Golish to talk about the leg pain component.

DR. KURSUMOVIC: Thank you. Adisa Kursumovic, neurosurgeon from Germany.

When I first got involved in this project and introduced Barricaid to my patients, I actually did quite some -- it's a new experience, because before I started working with Barricaid, it was either the question we do limited sequestration, we do limited discectomy, which I would do in 85% of cases. Or if it's a huge annular defect, you would go for aggressive discectomy. This was the very first time where I genuinely started looking for

annular defects, measuring annular defects and sealing annular defects in patient population with -- high-risk population with the large annular defects with Barricaid. Your question was about the proper placement of this implant and how does this implant work. The occlusion component is the mesh component, and that's the one that lies inside of the annulus. It lies on the end of the annulus and provides nucleus material to -- comes out of the annulus. And it is connected to the titanium anchor, which is implanted inside the vertebral body.

One of your questions was also where the titanium anchor ends or which part of the titanium anchor slides inside of the annulus, and that's just the anchor head. As you can see in these images, the whole titanium anchor is actually only there to securely fix the mesh. The whole idea about annular closure is not new. We know that Yashagrill (ph.) started in the '50s, and in the '70s, there were some attempts to do annular closure, but they all failed due to the high pressure inside of the disc space. So this would simply come out. So the occlusion component is the one that does the work that seals the annular defect, and it's only connected to this titanium anchor in order to be securely and to stay securely in place where it is.

DR. RAO: So the mesh is actually inside of the annulus?

DR. KURSUMOVIC: Mesh is actually on the end layer of annulus, yes.

DR. RAO: So the inner layer of the annulus.

DR. KURSUMOVIC: It's between annulus and nucleus, yes.

DR. RAO: Between the annulus --

DR. KURSUMOVIC: Yes.

DR. RAO: -- and the nucleus. So what's in the annulus is actually the titanium hub of the implant.

DR. KURSUMOVIC: It's just the titanium head, yes.

DR. RAO: Of the implant. So the occlusion is actually being done by the titanium.

DR. KURSUMOVIC: By the mesh. No, the occlusion is done by the mesh --

DR. RAO: Okay.

DR. KURSUMOVIC: -- which covers the annular defect from inside.

DR. RAO: So what's preventing the reherniation? Is it that you are restraining the nucleus, whatever we call the -- the central fragments of the disc, or are you sealing off the annular defect?

DR. KURSUMOVIC: That's the sealing of the annular defect and preventing nucleus to go out again through the annular fissure.

DR. RAO: Okay. So if you have -- forgive me for kind of -- I think it will be useful for the Panel to understand how you think the device works. So if we have -- so if you have, let's say, a 6 mm device, the thinnest of the lot, if you get an attempt at reherniation coming from either one side or the other side, how does that work? It's only a coaxial reherniation that this device will prevent, whereas clinically, we always, when we go in with our pituitary, we go with an up-biting and a down-biting because, you know, disc material can kind of extrude out from different directions.

DR. KURSUMOVIC: Well, the first request, in order to implant Barricaid properly, is to find annular defect, to visualize it, to measure it, and then to put this mesh occlusion component exactly in the defect. That's the main requirement for this implant to work.

DR. RAO: So what is your theory on why reherniations occur in 49.8% of people?

DR. KURSUMOVIC: To be honest, as I introduced Barricaid to my patients, I was hoping I will reduce the reherniation to zero. That was the goal, that was why I actually started, and I got very surprised why we had some reherniations in -- not only in the study, but in the real world as well. I believe that even with Barricaid, reherniations can occur, and that has to do with the disease itself. And with Barricaid in place, whenever we revised

patients for reherniations, we've seen that either the herniation or the new herniation was on the medial or lateral sides to Barricaid, so I believe that it's either that we missed to seal the defect properly or the defect enlarged over time. That's what I believe that's the reason for failure with Barricaid.

DR. RAO: Dr. Sayeed.

DR. SAYEED: In terms of pressure measurements, when you put the Barricaid device in, is there any increased internal pressure from the animal studies that you've recorded to date? If so, if there is an increase in pressure, that may explain the reherniation rate.

MR. STIEGMAN: No, we don't have any pressure measurements from the animal; however, I think that the pressure gradient that you described, and that seems sort of natural, is part of that root cause for that reherniation, even in the presence of the Barricaid device. It's too much pressure and it shoots out, which -- that's that.

DR. RAO: Just to get back to the basics again, if the device is working okay, how does that explain that the incidence of leg pain relief was not dramatically better?

MR. STIEGMAN: To address that, I'll call up Dr. Golish.

DR. GOLISH: Raymond Golish.

So I'd like to answer that question in two parts, please, and the second one will be encompassing a little bit of what Dr. Sayeed asked about other functional outcomes, including return to work, return to play. The data analytic explanation, as it's been explained to me, is that the functional outcomes and patient-reported outcomes are calculated, censored, based on the time-to-event analysis of the survival data, meaning when a patient has a secondary surgical intervention, they're already a failure based on the time-to-event analysis and the functional outcome scores, therefore, are calculated with those patients censored. That's a data analytic choice, as I understand it, often typical in the formal analysis of multi-component composite endpoints. And the goal, the rationale of

that approach, is to avoid conflating the response to reoperations with the event of reoperation itself, since reoperation is one of the outcome measures.

DR. RAO: I'm going to ask you to wait just -- Dr. Evans, I'm wondering what your thoughts are on the statistical aspects of that response.

(Off microphone response.)

DR. RAO: Do you have any more specifics, Dr. Golish?

DR. GOLISH: I'm sorry, I didn't hear the comment.

DR. RAO: Do you have any more specifics? He says he needs more specifics. What kind of specifics would you like, Dr. Evans?

(Off microphone response.)

DR. RAO: Could you give us your explanation one more time, Dr. Golish?

DR. GOLISH: Yeah. In fact, why don't I ask Greg Maislin to come up and give that explanation at a technical level.

DR. RAO: The question really is if the device is working at reducing reherniations, why is the incidence of VAS leg score not dramatically different in the investigational group versus the control group?

MR. MAISLIN: Sure. I'm Greg Maislin. I'm the principal biostatistician of Biomedical Statistical Consulting, and I'm Adjunct Professor of Statistics at the University of Pennsylvania School of Medicine, and I was the study statistician, and I'm representing the Sponsor.

The reason why the ODI and VAS scores are the same is because we censor at secondary surgical intervention. So we censored out the bad people, and what we're left with are the good people, and that's why they're the same. In order to fully interpret the VAS and the ODI data, you have to put it next to the proportions that actually fail.

DR. RAO: Scott, any thoughts?

(Off microphone response.)

DR. RAO: No, okay. Any other -- thank you.

MR. MAISLIN: Thank you.

DR. RAO: Dr. Sayeed.

DR. SAYEED: Could you get at that data a little bit easier if you had a true control, i.e., somebody -- you know, an arm where you didn't do any intervention?

MR. MAISLIN: I suppose if you had an arm where you had no intervention, you would get a population estimate of how these individuals do. Yes.

DR. RAO: Dr. Gilbert.

DR. GILBERT: I'd like to ask a material scientist's version of a statistical question, which means I don't know very much about statistics, but everything that has been reported, I think, and I want to know if my interpretation of this is correct, that everything reported in terms of survivorship appears to show benefit in the first 12 months, and that beyond 12 months, the rate of increased problems is equal for both, both arms of the study. So am I to interpret all of the statistical analysis to show that the benefits observed by Barricaid accrue in the first 12 months?

MR. STIEGMAN: Yes. The short answer is yes, you see a tremendous benefit of Barricaid within the first 12 to 24 months, and that benefit is maintained over time.

DR. GILBERT: I'm sorry, it's maintained in terms of the difference between, but the total failure increases so the -- you know, you folks talked about at 24 months it was a 50% reduction, but if you go out to 5 years, because they parallel, now that difference is smaller, the difference in survivorship is smaller as a percentage of the whole. So it's no longer 50%. Maybe it's, I think, 7% or something like that.

MR. STIEGMAN: Well, I mean, that's one of the big discussion points we've had with the FDA, is how to look at this longer-term data. You know, certainly we outlined various

limitations when looking at it in a cross-sectional manner. And according to the IDE for spinal systems guidance, I think there was confusion as to what guidance we were referring to, so it is the IDE spinal system guidance. It also says to look at it in a survivorship manner and truly, you know, provide the context and degree between these two. I'll call up Greg Maislin again, because I think he'll be able to explain it in a lot clearer terms than also a non-statistician could.

MR. MAISLIN: I'm Greg Maislin.

Yes, the benefit is primarily in the first couple of years, and then the two groups maintain over time. So there's two approaches that have been shown in the Panel packs. One is a cross-sectional analysis, and one is a survival analysis, and the cross-sectional analysis, that's limited to those that are theoretically due, and the terminal failures, as has been mentioned by both our speakers and FDA, the terminal failures are carried forward, but the successes aren't counted until the patient comes in. Moreover, you have to throw away 60% of the known safety events because it's limited to theoretically due.

So the survival analysis is the preferred approach, and I think most analysts would agree that when you're looking at long-term data, you should use a method that accounts for unequal follow-up, which the survival analysis does.

If you look at the screen over here, you could see that the difference between the two groups is maintained throughout the follow-up history. So at any point in time, the difference is about 10% for SSI superiority. So whether you're looking at 2 years or whether you're looking at 5 years, we know that there's a benefit.

When we looked at this difference in terms of numbers, NNT, the number needed to treat, which is a good measure of how we benefit patients, for reherniations the number needed to treat is 5, and what that means is that for every five patients that have this indication, we'll prevent one reherniation over the follow-up period. So I think that the

clinical evidence is that there is effectiveness and that it's maintained over the 5-year period.

DR. RAO: Dr. Maislin, I'm going to make it even more amusing for you. We had Dr. Gilbert's biomaterials knowledge of statistics, but I'm going to give you my orthopedic surgeon's knowledge of statistics with a question here.

You said you were censoring the patients that underwent surgery, and by censoring, I assume you mean removing those from the pool, and now you have the remaining pool that you're assessing, and in that remaining pool, the VAS leg score and the ODI was the same. Does that skew the overall interpretation of the study? Because you would imagine that that group needs to be included. If you're going to have a portion of patients that is not doing well, shouldn't that overall portion of patients be included in the statistical analysis?

MR. MAISLIN: Absolutely. And that's why we prefer to use composite clinical success endpoints, because in a composite endpoint you can't have an SSI and you can't have a reherniation. So among those individuals where you don't have an SSI or a reherniation, there needs to be some way to judge how well those patients are doing. So among those that don't have an SSI or reherniation, then we look to ODI and VAS and make sure that they also are large.

For the statisticians in the room, I know that there's only a couple, it's like a conditional probability. First, we look at the probability that you have an SSI or a reherniation, and then among those people who don't have that, we look to see did you have a good VAS and ODI, and you multiple those together, and you have a composite endpoint. So that's the purpose of a composite endpoint, is to appropriately combine the VAS scores and the terminal failure conditions.

DR. RAO: But in your modified composite score, am I mistaken in assuming that you

removed the VAS leg score from the assessment of the composite score?

MR. MAISLIN: This is a summary of the composite endpoints. The modified composite endpoint requires no symptomatic reherniation as a primary component. And then we look at those that don't have a symptomatic reherniation and ask, well, how did they do in their ODI? Did they do good? Well, you have to not only have no symptomatic reherniation, you also have to do good in your ODI. So it's a two-step process, and we keep those separate so we don't conflate the successful secondary intervention with a failed primary intervention.

DR. RAO: And what was the advantage or the intent of removing the VAS leg score from your modified composite?

MR. MAISLIN: We used ODI because it measures pain and function, but VAS, when you use VAS, you get the same answer. You could've used either one, and you get the exact same answer.

DR. RAO: Dr. Finnegan had a question and then Dr. Smith.

MR. STIEGMAN: Can I kind of further elaborate on that, because I think it was -- you made the comment, and I think it was another question earlier. When we were deciding whether we thought ODI would be more patient focused, or VAS leg, we really sort of debated that internally. Getting two questions from you guys and getting other questions, maybe VAS leg should've been used as opposed to ODI, but we looked at both within the same type of endpoint, and there was no effect. Both the ODI and VAS leg performed the same way, so the outcomes would remain the same.

DR. RAO: Dr. Finnegan.

DR. FINNEGAN: So my question has to do with the definition of SSI, in that recurrence of symptoms is a multivariable, and yet there does not seem to be any tests done other than the MRI, and how do you know that the MRI, which documented disc

herniation, wasn't an asymptomatic disc herniation and the symptoms weren't related to something else?

MR. STIEGMAN: To answer that, I think I'll call up Dr. Bouma to address the decision making for reoperations.

DR. BOUMA: Gerrit Bouma. I'm a neurosurgeon from the Netherlands and one of the investigators of the study.

Thank you for that question. That gives me the opportunity to clarify. The FDA has more or less implied that a physical workup was not involved in the diagnosis of the symptomatic reherniation, and that's not the case. Can you put up the slide for the classification?

A full physical workup including neurological assessment was completed preoperatively for all patients, and neurological assessment was uniformly performed as part of the diagnosis. As you can see, in the algorithm as developed by the DSMB, the positive straight leg raise test or a femoral stretch test was required as part of the diagnosis.

DR. FINNEGAN: How did you rule out other variables, which are very common in recurrent symptoms in low back and lumbar spine issues?

DR. BOUMA: Which variables are you referring to specifically?

DR. FINNEGAN: So to facet arthropathy, other level discs.

DR. BOUMA: Of course, the decision to assess whether a reherniation was symptomatic and whether surgery was required was a decision that was made by the physician in discussion with the patient. It was always a shared discussion, decision making. And no surgeon in his right mind would reoperate for a herniation that he considers to be not related to the symptoms of the patient. So this was all taken into account. But the protocol of the study did not control for all of these aspects, but that was left to the

discretion of the surgeon as in any spine device trial.

DR. RAO: Dr. Smith.

DR. SMITH: Just a question and a comment, and I'm not sure if you have any data on this, but a lumbar disc herniation is probably one of the better surgically studied diseases we have, both long-term operative and non-operative course, and generally, the goal when we do a primary surgery is to get the individual back to work more quickly, back to quality of the life. And then 5, 7 years later, the results tend to regress towards the mean for operative and non-operative treatment.

Looking at other device trials, not representative specifically, but there have been other trials where individuals have talked about reoperation rates, reoperation rates of one device compared to another, and a criticism about confounding is when the surgeons involved in the trial are the surgeons making the decision to reoperate, there may be an inherent bias about taking the device back to the OR. I'm not saying that was or wasn't the case here, but that was part of my earlier question about whether there is any defined protocols for when to reoperate.

And then we're sort of aliasing outcomes about how the outcomes were, but if the primary goal of the device is to prevent reherniation and there's a significant reherniation rate, and then if the device in your data has a 10% failure rate, it's hard for me to reconcile those numbers. And the mitigating factor is, well, we know that when folks go back to the OR, in your data there's a higher rate of secondary surgical operations in the control arm, and so therefore you're postulating that your device is safer than control, but yet your investigational surgeons were the ones who were making the decision about whether to reoperate. And so that's an inherent set of confounders that I'm having a hard time reconciling.

MR. STIEGMAN: So there was a lot of points and I believe a question there. And

one, you know, the Sponsor -- we're not going to tell the surgeon when to reoperate. I mean, that's his decision along with the patient. But at the same time, it goes back to that composite endpoint. If they're biasing somehow when to reoperate/when not to reoperate and the patient is in pain, it's going to show an effect within the ODI scores, the VAS leg scores, maybe the neuro assessment, it will show somewhere else, which is a good equalizer to any perceived bias within the decision to operate. The decision to reoperate within this study, there was a similar proportion between the symptomatic reherniations that were reoperated; there was a 53.5% rate in the Barricaid and a 60.8% in the control. So those are approximately equal, so there was no bias towards Barricaid, in any fashion, because there was a device or not a device or what arm they were actually in.

As far as, you know, the integrity rate or reoperation, device-related reoperation rate, you know, we did provide a table that was -- showed that rate or at least showed the device integrity over a 5-year period, and you saw it go down from -- many of the device integrity findings were asymptomatic, and those that weren't, it was very small; it was eight with all the data out to 5 years. And if you compare that to the benefit that we show with -- the benefit in that gap that we showed at the very end with the symptomatic reherniations compared to what Barricaid is providing, as well as surgical interventions and then the SAEs, and the SAEs is a true, sort of, foundation trying to demonstrate safety and effectiveness of this device. Essentially, this particular category should catch anything with device integrity that's clinically important. It will catch anything that's related to EPCs because, obviously, that's a big topic. And you still have that maintenance of the benefit.

So, yeah, I mean, some of your points are well taken. I think, in general, if you look at all of those components and all of those factors over the course of 5 years, there is actually a good safety and effectiveness benefit.

DR. RAO: Dr. Smith, you had a second question, just go ahead.

DR. SMITH: Just a quick follow-up. Yeah, I'm not implying there is any inherent bias. It's more just, I guess, as a clinician, if I do a microdiscectomy on a patient and they reherniate and they have leg pain, I have a relatively low threshold to reoperate if I can't resolve it non-operatively, whereas if it's a device where Dacron mesh is flipped out on the foramen and the revision is more complex, it may subtly, not intentionally, but it may inherently bias towards trying more non-operative treatment before going back.

And then the only other caveat is a safety perspective. If it's a 10% -- and correct me if I'm wrong, but if it's roughly 10% failure rate and maybe asymptomatic, but at the time, I don't know if we fully understand the long-term ramifications of having a piece of Dacron mesh against the dura in a 40-year-old and just, long term, that -- generally, the dura doesn't do well when things are laying up against it over a period of years. It has a tendency to -- things happen.

DR. RAO: Okay, I'm just going to -- Ms. Starowicz, I had cut you off before lunch. If you'd like to state your question now, and then we'll go to Dr. Sayeed.

MS. STAROWICZ: Sure. Thank you very much.

I think my question was regarding, I think, on FDA's presentation you have a slide that talked about benefits and risks, and then the risks, I think there was specifically a notation around bone necrosis and resorption, and my understanding is that this would be an assessment that was done by the third party or the DSMB. And so my question was in terms of if they were looking at endpoint changes, what categories, I guess, were on the form for them to be able to select? In other words, what determined something being noted as bone necrosis/resorption versus perhaps some other endplate change?

MR. STIEGMAN: Sure. So, to discuss this, I'll bring up Oscar Yeh.

DR. YEH: I'm Oscar Yeh, Vice President of Research for the Sponsor.

The case report form for the adverse events had that specific wording "bone

necrosis/resorption." As the investigators observed these endplate changes, they found that that term was the closest one to what they would want to select to report that radiographic observation. So, you know, perhaps a poor choice. I don't believe there's any necrosis actually observed, but that was the closest term they could select.

MS. STAROWICZ: So it was a synonym for endplate change?

DR. YEH: Correct.

MS. STAROWICZ: Thank you.

DR. KATZ: I actually have a follow-up on that related to the DSMB. The DSMB reports to the Sponsor, and I'm wondering, at the review, was information from the radiology, the independent radiology group, presented to the DSMB? Did they know about these endplate changes or endplate lesions and report it back to the Sponsor? And then what determined the safety or the effectiveness to let the project continue?

MR. STIEGMAN: Sure. So I'd like to call Oscar Yeh back up again.

DR. YEH: Yes, the DSMB was fully aware of all the endplate change data that was coming from our core lab. This was true when endplate changes were first observed in our feasibility studies prior to the project we're talking about today, where, in fact, the DSMB met at the core lab to become fully aware of those assessments. With each of our large data exports and looking at the data received by -- received from the core lab, we did share the data, the rates. There was special sessions in which we specifically discussed endplate changes only and its clinical correlation as well.

DR. RAO: Thank you.

Dr. Sayeed, you had -- no. Dr. Graf.

DR. GRAF: Getting back to my question that I asked before the break, I'm just having a hard time grasping regarding the annulotomy once again, because some different numbers have been presented. You know, at 2 years you're demonstrating that Barricaid

has an 11% recurrence rate versus the control of 25%. You know, if you look at the SPORT study, it's much, much lower, around 8% recurrence rate, and my fundamental question is, is the recurrence rate of your demonstrated disc herniations in your control group due to a large annular defect which has been created? And you documented that's about 40% of the cases where these are newly created annular defects. In my mind, of course, if you're taking two sets and making a large annular defect, of course, the recurrence rate is going to be lower, but is that really going to be played out into what we truly operate on and don't necessarily create a large annular box defect when we typically perform these surgeries?

MR. STIEGMAN: Sure. And thank you for getting back to some of the first questions. That is an important question, and I want to make sure because, as we saw today, the FDA's presentation and questions to you guys will heavily generate around the appropriate population and what that may be. And this is a piece of that puzzle. You know, I want to make clear, and I think after I show some of these numbers, and hopefully it's clearer to you, the exact numbers of these patients. I'll bring up Dr. Kursumovic, who's actually performed the surgery and gone through this sort of mental checklist.

So this is what was presented earlier, and you see the 39 and 35%, and I believe that's the numbers you were referring to. But then, also, you see the box and the other, and you know, if you talk about the bias component, you would actually imagine box would be higher in the control group if, theoretically, that was going to create a higher reherniation rate. But you see that this is -- the box in this particular category are both through the existing defect and create a new defect. So if I could get the new box. Just the values. And you'll see, in a second, that the box created new was actually 26%. So it wasn't as large of a population, therefore having really a minimal influence on the overall reherniation rates. They may get it up in a minute, but I'd like to also talk to -- let Dr. Kursumovic discuss her findings.

DR. KURSUMOVIC: I definitely can confirm this. The majority of the patients where we implanted Barricaid, or which were in the study, were assessed or approached through the existing defect. So it was just a smaller portion of these patients where the surgeon thought that he needs to do annulotomy in order to decompress, precisely, and in these cases he was -- he needed to do the smallest annulotomy possible, and he would seal this annulotomy he has done. But the majority of the patients was approached through already existing defects.

DR. GRAF: I appreciate that, but the number is still 40%. That's not small in my mind.

DR. KURSUMOVIC: Forty percent of our surgeons thought that they need to do some kind of annulotomy, and they sealed this annulotomy defect good, in order to decompress the nerve root properly.

DR. GRAF: Can you go back to your previous slide real quick? It was 39% in the control group, though. Those weren't subsequently sealed, though.

MR. STIEGMAN: Correct.

DR. GRAF: Correct. I just want to point that out.

MR. STIEGMAN: Yeah. But I mean, we also have to remember, one, you know, this is a new defect, so it could fit in one of any of three categories, and the three categories were a slit, cruciate, or box, and by the definition of box, really, there was anything that was relatively open, that didn't fall into the other two categories, were sort of a wide net of options. So it wasn't, you know, the quintessential box annulotomy for a cage, as you referred to and as well the FDA. It was simply a defect.

DR. RAO: Thank you. I think we're kind of back on track, so we'll let you get back on track and kind of start -- continue responding to the questions that were raised earlier this morning.

MR. STIEGMAN: Thank you. There were a lot of questions from the morning, and even though my handwriting was inedible and illegible --

(Laughter.)

MR. STIEGMAN: -- we did figure out a way to organize it somewhat. First, there was a discussion regarding -- and I'm just going through some of the questions that have already been answered -- the location of the endplate changes in relation to the anchor. I don't have the name written down. Can I get AA-29? So the breakout of EPCs by endplates and the device orientation as outlined in the surgical technique, it can be placed superior vertebral body or the inferior vertebral body, so that's the relationship to the device orientation. And then you see superior, inferior, and the number of EPCs in those associated areas.

DR. RAO: So what's the interpretation of this? So the interpretation is it's not correlated to the base plate and not correlated to the mesh?

MR. STIEGMAN: No. I think, in general, the location of the EPCs were opposite of the anchor. So if you remember the technique, you know, the anchor goes in one side and the mesh is on the other. It's on the other.

DR. RAO: So generally on the mesh side?

MR. STIEGMAN: Correct. Then we got into a bunch of -- I guess does that answer that individual's question? So then we got into -- it goes along with the inflammation question and the appearance of birefringent crystals, negative or positive. I'd like to call up Dr. Lalor to address that.

DR. LALOR: Good afternoon. My name is Peggy Lalor. I am the president and CEO of Histion, and I'm the person who was responsible for analysis of the retrieved tissues from the Barricaid study.

In response to the question about the crystals, there were no crystals seen in any of

the retrieved tissues, and therefore no analysis for elongation, positive or negative, was completed. We did see particles, and I can go into that now, if you'd like to, or I can take that a little bit later, with respect to the additional questions that you had. Which would you like me to do?

DR. RAO: Dr. Gilbert says he wants them now.

(Laughter.)

DR. LALOR: Okay. I can go through my findings of the analysis. We had 11 tissues that were available for histology.

DR. RAO: Is this tissue, or is this particles, because is -- was that tissue specimen or is it just --

DR. LALOR: This is tissue that came from the retrievals. And I had --

DR. RAO: Do you get lots of tissue, or do you get mostly the implant?

DR. LALOR: There was some implant; there was some tissue. It was not a homogeneous amount of any one tissue type. There was some of the mesh material, there was some fibrosis, there was some nucleus pulposus material, a little bit of annulus, some bone in various concentrations and amounts in each of the patients' tissues, of those 11 retrievals.

DR. RAO: Because we were told this morning that there was no attempt made to gain any additional tissue during the retrieval. It was just that the implant was taken out, and whatever tissue came with the implant, I presume, is the tissue you're talking about.

DR. LALOR: Or around or whatever they removed. I don't know exactly what location those tissues were taken from. I received tissues that were basically from the retrieval, and they said please analyze them for me. So what I did find is that in those specimens that had portions of the mesh, I saw mostly nucleus pulposus material, nucleus pulposus cells, and little to no inflammation at all, except perhaps at the edge. There was

one example that was shown earlier today, where you did see quite a large number of macrophages and giant cells, and I think that is a -- that was a unique circumstance, and I believe it was taken from one of the examples I'm going to show you a little bit later, and I can confirm that after the break. But let me go back, first of all, to say that overall there was no evidence in any of the tissues for infection. And I did see, as I said earlier, some fibrous tissue, certainly some inflammation within the fibrous tissue, and that was focal and in most cases not very extensive. But I would like to show you some examples of one -- two, in fact, where there's a bit more extensive inflammation overall in the tissue.

This first example, you can see that -- no, that's not the right slide. Can you go back, please? Oh no, never mind, I'm looking at the wrong -- I'm looking at the wrong monitor, please excuse me. If you can see, this is from one of the patients where there was a bone fragment, and we had bone fragments in many of the retrieved tissues from many of the patients. And in this instance there were particles, and I would expect to see particles in a retrieval, particularly with a polymeric device, and those particles are seen, on the left-hand side, under polarized light as birefringent material. If we were to look closely, we would see those and macrophages and some occasional giant cells. What is important to note is the fact that there is no active osteolysis, no osteoclasts, and no scalloping indicative of previous osteoclast resorption of the bone, even though there is some inflammation next to the bone.

In another case that I have up here now, you can see, on the left-hand side, a fragment of bone that shows that there was some evidence that bone is lost in the trabecular structure. You can see it as the round circle in the far left. At higher magnification, which you can see on the top, rather, to the right, you see that it's fibrous tissue and not inflammation. There's not a substantive amount of macrophages and giant cells or particles, for that matter, which you can see on the left-hand side under polarized

light. So what I have determined from my analysis is that there is no evidence for particle-induced osteolysis based on the retrievals that we had at hand.

DR. SAYEED: Just in follow-up to that, where were these bone fragments? You know, are they taken from the anchor side, or are they taken from the mesh side?

DR. LALOR: They're actually just taken from the area that the surgeon can see when they go in there to look at the situation, but I would have to ask the clinician to come up and discuss a little bit further where these might have come from.

DR. WEISBRODE: Can you explain the appearance of what looks like reverse image of thread on the image, the top left?

DR. LALOR: I'm sorry?

DR. WEISBRODE: What looks like the reverse image of what we see when a screw is put into bone, there's a thread-like -- the negative image of a thread-like thing on the image at the top left.

DR. LALOR: I don't believe that comes -- oh, I see what you're saying.

DR. WEISBRODE: That doesn't look to me like a spontaneous fractured specimen. That looks like that's been removed by some kind of -- you see what I'm getting at? There's this image of the scalloped circles.

DR. LALOR: It could be bone directly in contact with the anchor.

DR. WEISBRODE: Oh, okay. Thank you.

DR. RAO: Dr. Finnegan.

DR. FINNEGAN: How long were these specific images implanted, specimens, how long were they implanted?

DR. LALOR: Give me 2 seconds. I have that written down. One of them was implanted for 2.9 years and one for 3.6 years. The first one was 3.6 and the second one I showed, which is -- currently is 2.9.

DR. RAO: Dr. Subhawong.

DR. SUBHAWONG: Ty Subhawong.

I just want to make a comment, that even though we're not seeing, maybe, histologic evidence of osteolysis, I think radiographically we saw fairly convincing evidence that there was osteolysis, particularly with the subtype of lytic lesions that Dr. Amrami showed that had a poorly defined or poorly -- or non-sporadic margin around the area of osteolysis. To me, that looked like active osteolysis.

MR. STIEGMAN: And I think we'd like to address that point as well. I'd like to call up Dr. Mark Schweitzer.

DR. SCHWEITZER: Thank you. Mark Schweitzer, musculoskeletal radiologist. I'm from Stony Brook.

I agree with Dr. Amrami that there were three types of endplate changes. When the core lab evaluated for endplate changes, they just evaluated them in general, so we needed to retrospectively go back and try and differentiate the different types of endplate changes. The first type is the irregularity that you see following discectomy, in the literature, roughly 50% of cases. We've seen roughly equal in the Barricaid and control groups. We'll dismiss that as typical postoperative findings.

The second part, endplate lesions described by the FDA, Schmorl's nodes, again seen in both populations, well known in the literature not to be a major issue, and we'll dismiss that.

The lesions in question are what the FDA refers to as lytic lesions. To try and separate those out, we used the lesions that were in proximate location to the mesh, and a fraction of them had mesh subsidence. Those lesions on MR showed very little marrow edema. The marrow edema tended to be early and go away almost always; at the later time points, had areas of sclerosis surrounding it that developed in the intermediate time

points and evolved over time. I feel quite confident that they're not -- that does not represent particle disease. If we talk about bone lysis being any evidence of bone loss, then I'll agree that it's osteolysis bone loss.

Presumably, on a mechanical basis, the Barricaid device is a dynamic device. There is recurrent pressure, that's the intended function of the device. So likely a fraction of patients will develop these changes mechanically. The changes do evolve relatively quickly, and at the later time points, on average, the largest lesions actually have a mean loss of size rather than increase in size. So they appear to be an early biomechanical adaptation to the placement of the device.

DR. WEISBRODE: Steve Weisbrode.

Would you make the -- I'm not sure if you had a chance to look at the baboon studies, but would you make the same claim about the lytic lesions of the baboons?

DR. SCHWEITZER: My understanding of the baboon study is the device was markedly mal-sized for the baboon intervertebral disc space.

DR. WEISBRODE: Let me interrupt. My question is do you think -- do you feel or don't feel that the mesh was significantly related to the loss of bone lysis and may have played a role, other than other mechanical factors, in the baboons?

DR. SCHWEITZER: Well, I think they -- to me, the mesh is causing a mechanical reaction with bone --

DR. WEISBRODE: Okay.

DR. SCHWEITZER: -- with some remodeling. I think it was marked in the baboon study because the device was probably 2 to 2½ times the size of what it should've been for the baboon.

DR. WEISBRODE: But again, it's the concept that the mesh may be able to cause bone lysis.

DR. SCHWEITZER: Well, I would call it mechanical adaptation. You know, bone is a dynamic structure and will respond to stresses and will adapt to them.

DR. WEISBRODE: Lysis is not one of Wolff's law.

DR. SCHWEITZER: Well, it is a pressure point.

DR. WEISBRODE: Okay, thank you.

DR. RAO: Thank you, Dr. Weisbrode.

Dr. Katz.

DR. KATZ: Before we let Dr. Schweitzer go, do you think that you could show us some of the MR studies that we've been asking for?

MR. STIEGMAN: Yes. Thank you, Dr. Katz. I was going to say the same thing.

DR. SCHWEITZER: Yes, we have them. So on the upper part of the slide that you see are CT images going from preop to 5 years, and this is a patient that I think we can -- can we go back to the previous?

(Off microphone response.)

DR. SCHWEITZER: Sorry. And this is a patient who has a lytic endplate lesion, and we can see that in the upper aspect of the L5 vertebral body. If you look at the MR, you see a little bit of surrounding marrow edema, mostly at the 2-year time point. At the 4-year time point, it's basically gone away, and at the 5-year time point, you see sclerosis on CT and no marrow edema on MR.

Of note to the Chairman, Dr. Rao, you can see how the disc is well seen and that the placement of the device would in no way interfere, in my opinion, with a diagnosis of a recurrent herniation.

DR. RAO: Thank you. Just stay on that same slide for just a second. If you look at the CT on this patient, it almost looks like there's some level of fusion posterior to the implant, and I wonder if that fusion provides some stability which then allows those MRI

changes to sequentially get better over the course of time. Do you see the fusion I'm referring to posteriorly?

DR. SCHWEITZER: I see some new bone formation posteriorly, particularly at the inferior aspect of the device. All I can comment on is that there is relatively little marrow edema, even early on before you see that, which to me is a manifestation of a relatively minimal biological inflammatory response to the device.

DR. RAO: Thank you. That's very helpful. Thank you. If we can see the other patients. Dr. Katz is anxious to see the other four.

DR. KATZ: Mark, if you could just go back -- sorry, Dr. Schweitzer.

DR. SCHWEITZER: Yes.

DR. KATZ: Just one slide where you were. I'm just interested in the 5-year picture from the CT and the MRI, because the low signal that we see in the top of the vertebral body is not really correlated with the lucency that we see on the CT. So it's not sclerosis.

DR. SCHWEITZER: Well, the low signal --

DR. KATZ: I mean, the rim is sclerotic, correct?

DR. SCHWEITZER: Yes.

DR. KATZ: But the cavity --

DR. SCHWEITZER: Oh, got you.

DR. KATZ: -- is loosened --

DR. SCHWEITZER: Yeah.

DR. KATZ: -- on the CT and it's not loosened -- you know, it's not really -- it's dark on the MR. So what material do you think that is?

DR. SCHWEITZER: Well, like Dr. Lalor just showed, I believe that that's fibrous tissue forming in the defect. The MR signal characteristics are consistent with that, as you pointed out.

DR. RAO: Dr. Smith.

DR. SMITH: Just to follow up on a comment of Dr. Rao's, and also I believe Dr. Wang made a comment in the last session. There was flexion-extension x-ray data, presumably for these patients. Is there any information on the segmental motion of these inner spaces over the postoperative course, because that would help to address if there's -- regardless of the CT appearance, that there's functionally a fusion or not within the radiographic definitions.

MR. STIEGMAN: Yes. Yes, we have that information. Let me pull this up.

DR. RAO: We could maybe go to that later. Why don't we see --

MR. STIEGMAN: Yeah. Yeah, we can pause that.

DR. RAO: Why don't we see the few patients from the MR?

MR. STIEGMAN: The short answer is yes, we have that information, and yes, it maintained motion.

DR. RAO: But we will come back to that, Dr. Smith, and we'll look at some flexion-extension.

DR. SCHWEITZER: So we're going to go back to --

DR. RAO: The long-term longitudinal follow-up imaging studies.

DR. SCHWEITZER: So this is a control patient, and again, the upper row is the CT, the lower row is MRI images. This patient has two large lytic lesions on either endplate, a larger one on the superior endplate. To me, this is somewhat more than a Schmorl's node, and the evolution, I would call these lytic changes by the FDA's criteria. They started relatively quickly at Year 1 and show similar characteristics on CT, which some are more sclerosis up to Year 3, and you see like the tree, a trunk appearance on MR, particularly Year 3, which is showing gradual changes as it evolves over time. So the MR shows evidence, also, of ongoing evolution of this change in the control patients. Although there were larger and

more lesions in the Barricaid patients, the single largest lesion was in a control patient. And this patient did very well clinically. No, I'm sorry, did very poorly clinically, had reoperation for reherniation.

DR. RAO: So some of those changes could be after the reoperations also?

DR. SCHWEITZER: Yes.

DR. RAO: Okay. I think we're mostly interested in seeing how the implant does with time.

DR. SCHWEITZER: I think we have one more example. So this is another Barricaid patient. Again, upper row is CT, lower row is MR. You don't see the anchor on these images because we tried to pick the sagittal image that best showed you the marker where the mesh is. And you can see that there is this development of an endplate lesion in the lower aspect of the upper vertebral body at Year 2 and enlarging at Year 3 and then decreasing size at Year 4 and Year 5. At least on CT. And again, it will also demonstrate that the disc is well seen, even with the Barricaid device, adding credence to the ability to diagnose recurrent herniation.

DR. RAO: Any other patients?

DR. SCHWEITZER: Those are the ones we had prepared.

DR. RAO: Dr. Katz, any thoughts?

(Off microphone response.)

MR. STIEGMAN: So back to flexion-extension, so these are the rotation over time, which is the flexion-extension. These are added numbers, and you can see, there's really no trends to speak of, you know, looking at degrees of between, you know -- hovering between 1 degree through all of these time points. And then we also have translation showing no instability and how that stabilizes.

And there was also a question about posterior ossification. I can pull that up as well.

And if you look at qualitative assessments of posterior -- and please, just stop me. I'm just going to keep going. There's more questions to get through. The posterior ossification, again, you can see sort of the same trend as the translation. It stabilizes over time in both groups.

Flipping through these questions, there was a question about conservative care from Dr. Sayeed. We don't have the various conservative care -- type of conservative care that, you know, eliminated the patient or screened them out. I can say that there was 470 patients out of that 3,300, initial 3,300, were screened out because of less than 6 weeks of failed conservative care. That's all the information I have.

There are two FDA questions that we were tasked with. The by site, site-by-site variability. And this was noted in the FDA's Executive Summary as well as ours, that there was no site-by-site differences, and here's a table it breaks down. You can see the relative consistency that was also mentioned during the morning discussion of sites. You know, there is not a tremendously large site, and you're always -- obviously, in every study, you're going to get a couple of smaller enrollers, but a pretty good, consistent enrollment rate across the board, and then no variability.

And then the last FDA question I believe we were tasked with dealt with fusion and whether or not if they converted to a fusion or reoperated and chose to have a fusion, there was no difference, well, no difference, but any hindrance or increased effort to fuse them, and the answer is no. The success rates with fusion was the same. The amount numerically was higher in the Barricaid group, but that was between -- I think it was 21 and 17 patients that got a fusion. The preoperative and perioperative outcomes of those that fused in the control group versus those in the Barricaid group were also not different. No new or increased intraoperative AEs, blood loss, OR time; all of that was the same for the fusion group in the Barricaid group compared to the fusion group in the control population.

And hopefully that answers that particular question.

DR. RAO: Was the type of reoperation roughly the same in the two groups? Do you have data on what was done in the -- you may have presented it and I may have missed it, but the type of reoperation that happened over the course of the 5 years?

MR. STIEGMAN: You mean the type of fusion or type of just --

DR. RAO: No, the type of reoperation in general.

MR. STIEGMAN: In general.

DR. RAO: Was it just, you know, a repeat disc removal or repeat disc removal with a facetectomy, repeat disc removal with facetectomy with posterior fusion, interbody fusion?

MR. STIEGMAN: I think to answer that, I'll call up Oscar Yeh again.

DR. YEH: Yes, in general, the types of reoperations were the same, but I think your question was more about the proportion. Because the Barricaid group exhibited fewer reoperations overall, some of those proportions look different than those we've discussed and had been asked by FDA about the fusions in particular. While the overall numbers were very similar because there are fewer reoperations in the Barricaid group, it's expressed as a larger proportion. Our interpretation of that is that the reasons that one might perform a fusion post-discectomy remain, that the Barricaid device doesn't necessarily address those, and so that number of overall fusions remains similar.

DR. RAO: Do you have any data on what the types of operations were in the two groups?

DR. YEH: Yes, we certainly do. So the largest category --

DR. RAO: If you could show us the slide, that would be -- if it's on a slide form, by any chance.

(Off microphone comment.)

DR. RAO: It wasn't yours? If we could have the slide, that's fine.

DR. YEH: Yeah, if we could get the slide from --

DR. RAO: Slide 47 from FDA, Dr. Elder says.

MR. STIEGMAN: Dr. Rao, this one, correct?

DR. RAO: This one? Thank you, yes.

DR. YEH: Right, correct. So we've put them into similar categories. But it also notes in those discectomies whether removals have been performed, and some of those are partial removals where just the mesh is removed or a whole device removal. And the same there with supplemental fixation, it's just giving additional detail on what else was performed. So they've been all grouped together there, but the large -- yeah, the majority are discectomy procedures. There are these supplemental fixations; there are some of these others that are also distributed pretty well in terms of wound revision and hematomas.

DR. RAO: Dr. Elder.

DR. ELDER: Ben Elder.

I think my question is more related to if these supplemental fixations were posterolateral fusions or interbody fusions, and for the ones that were interbody, were there any increased risks with removing the device as well as with some of the lesions on the endplate having an increased risk of subsidence of your graft?

MR. STIEGMAN: Sure. I'd like to call up Dr. Kursumovic to discuss that.

DR. KURSUMOVIC: Adisa Kursumovic.

All revision strategies for this implant are possible. In the cases of interbody fusion, I think the only option where you should consider removing the whole implant before going forward would be a PLIF cage. Otherwise, ALIF is possible. You can do it in a way that you leave the implant completely in or just remove the mesh. Or TLIF from the other side would be possible as well. In cases of endplate lesion and especially large endplate lesions, I

would suggest to use the cage with the larger footprint. And just in case of PLIF, it would be necessary to remove the implant completely because the implant is in the place where you would want to have your second PLIF cage. But all the revision strategies are possible, and there was no increase in any complications related to removal of the implant.

MR. STIEGMAN: All right. Moving on, there was a question regarding any data, the difference in data between age and sex. That was one of the initial, I believe, questions. So we examined the differences between or within the groups, between age based on the median age and sex. There are no statistical significant differences in the composite primary endpoint, reherniations, symptomatic reherniations, secondary surgeries, or SAEs for age. There's just nothing between the younger population and the older population. For age, you see this, where the younger population, there was a signal or chi-square p-value of 0.005 for symptomatic reherniations, with the group being 82.4% for the lower age group. You see no difference between the control. Sorry, go ahead.

DR. RAO: Ms. Rue.

MS. RUE: This is Karen Rue.

You don't have anything broken down more, like to 20-year-olds and over 65 rather than just less than 43 and over 43?

MR. STIEGMAN: I don't believe so. Just that there were no trends for the older population and younger population. I'm sorry.

I think -- and maybe -- yeah, I think that's it. I'm going through all my pages, and maybe I missed one.

DR. RAO: Dr. Katz.

DR. KATZ: I was wondering, did you ever have a chance to get any of the MR data on the baboons? I'm having some issues trying to reconcile between the controls and through the operative patients because Dr. Schweitzer showed, you know, it was very good, but it

was low signal, which in the controls, I'm trying to figure out what that was. Unless that's maybe disc material that's herniating, you know, into the vertebral body. So I'm just wondering, also, did you have -- because the baboons, it said in the study that there was both CT and MRI. So do you have any of the MRI on the baboon study?

MR. STIEGMAN: Yeah. I think to answer that, I'd call up Oscar Yeh again.

DR. YEH: I apologize, I'll have to answer that in a moment. We do have baboon MRs. I'm just talking to our back room about getting those images up.

DR. RAO: Dr. Sayeed.

DR. SAYEED: While Dr. Yeh was -- my question is regarding the device, the device movement into cord or nerve root, any MRI evidence of enhancement or signal attenuation.

DR. RAO: I'm not so sure the question is clear, Dr. Sayeed.

DR. SAYEED: Yeah.

DR. RAO: Could you rephrase that question?

DR. SAYEED: Yeah. So the FDA had mentioned that there was MRI evidence of device -- when there is device migration, that there is enhancement on MRI of nerve root and spinal cord enhancement by MRI. Do you have any pictures or any images that indicate this?

(Off microphone response.)

DR. RAO: We can't hear you, Doctor.

MR. STIEGMAN: I will answer. From what I heard, no patients got contrast, and she reviewed that.

DR. RAO: Do you, by any chance -- while we're talking about imaging, do you, by any chance, have any axial MRI images to show us what reherniation looks like? I don't think we've seen a single axial image with reherniation in a device group, and it would be very interesting to see what axial images look like for reherniation when there's a device already

implanted. If you have a couple of images, that would be great to look at.

MR. STIEGMAN: Sure. I think, yeah, maybe we're due for a break in a little bit, and I can get it right after that break.

DR. RAO: Preferably before the break, if possible --

MR. STIEGMAN: Okay, absolutely.

DR. RAO: -- because after the break is for the specific questions.

MR. STIEGMAN: For your discussion, yeah.

DR. RAO: Dr. Smith.

(Off microphone comment.)

DR. RAO: On a different topic, he says. That's a warning.

MR. STIEGMAN: Right.

DR. SMITH: Just as a follow-up about the biomechanical question. And I don't know if you have any of the data even to show easily today or not, but my understanding -- and I don't know if it would be better to call it an annular plug device than an annular closure device, but this Dacron bag goes in and it's anchored, and then it undergoes basically repetitive loading cycles over the duration of the implant's existence. And the data that I see here, from reading what you've presented and submitted in the summary, the most common mode of true mechanical failure was the plug or the Dacron mesh detaching from the anchor, correct? That was the weakest point of the implant.

In the mechanical testing for the occlusion component detachment, the only testing data that I see for testing it to failure was 50,000 cycles. Even a sedentary person walks 5,000 steps a day, so 50,000 cycles would be 10 days. I'm having a hard time to understand did you guys do any bench-top testing to failure with a number of cycles that are approximate to lifetime of the implant and the mode of failure that you've identified as the most likely mode of failure?

MR. STIEGMAN: Yes. Yeah, we did, and that was actually one of the questions I may have forgotten, because it was asked by someone else earlier. I'll call up Oscar Yeh to address that, thanks.

DR. SMITH: Okay, thank you.

DR. YEH: Oscar Yeh.

And maybe we can answer this in stages. I'm going to describe the preclinical testing that we performed when we received the CE mark prior to start of this trial, and then the specific testing that you just referred to is actually testing that was performed earlier this year, where the goal of that testing was really to recreate failures. So just to put that in context and why the model was so aggressive.

So prior to the start of the study, we did a variety of different tests. I think you're probably most interested in the fatigue test, and so I'll describe those. We had testing where we simply bluntly applied a lateral force to the anchor for 10 million cycles. The load was about 35% higher than what we calculated to be the max load we would expect based on literature, based on the intradiscal pressure.

The cyclic nucleus pressure testing was a test in which we had a simulated posterior geometry of the disc. We had our device implanted. We used silicone beads that were lubricated to facilitate mobility. Those were pressurized to -- in this first iteration of the test, it was pressurized to 23 atmospheres, so that's the highest reported intradiscal pressure in the literature. We did that for 10 million cycles, and I think that's kind of addressing your main question there. So we have the model set up, and the beads are being forced against it for 10 million cycles without any migration or failure.

And then the last cyclic test was cyclic compression shear testing where this was really to look at, sort of, the worse case of a complete collapse. Where it differs from the typical ASTM testing is that we used bone foam to simulate the actual -- this is a bone foam

that actually was custom made with a harder endplate surface than any softer underlying trabecular bone, and we subjected the device to 10 million cycles of that as well. What we saw was subsidence of the anchor head, but the mesh remained attached, and the anchor head was -- there were no device fractures, either. So that was the preclinical testing that gave us the confidence to go into the trial. As we learned, and as you noted, we saw some migrations and some detachments, and to describe that effort and what was in the Executive Summary from FDA, we'll bring up Ryan Siskey.

DR. RAO: Dr. Gilbert had a follow-up on that, Dr. Yeh, if you could just stay there for a minute.

DR. GILBERT: Yeah, just to make sure I understand. So the compression shear testing, you're saying that's there bone foam, polyurethane, probably --

DR. YEH: Correct.

DR. GILBERT: -- made direct contact to the titanium top where the fiber is interposed, and then you did shear for 10 million cycles. And what was that contact load that you used?

DR. YEH: Oh, we used the standard, so we used 1,200 newtons.

DR. GILBERT: You did, okay. Thank you.

DR. RAO: Dr. Elder and then Dr. Donshik.

DR. ELDER: I just wanted to go back to the previous discussion of the reherniation. I just had a question on -- in your definition of it, you described that the surgeon could rule out that it was a reherniation by calling it residual nucleus material, and I was wondering how the surgeon would differentiate residual nucleus from reherniated nucleus.

MR. STIEGMAN: If the Chair allows, I'd like Ryan Siskey to fully answer Dr. Smith's question, unless he's satisfied with that description.

DR. RAO: Sure. I mean, whatever answers the question best.

MR. STIEGMAN: I mean, it's up to you guys. You guys are -- well, I just want to make sure I get to all of the questions.

DR. RAO: Sure, let's get to that question.

MR. STIEGMAN: Okay.

DR. RAO: Let's get to that answer.

MR. STIEGMAN: Ryan Siskey, please.

MR. SISKEY: Can we repeat that question? We're going back to the pre-clinical testing, post-clinical testing?

DR. RAO: Go ahead. Which question were you talking about? You were talking about Dr. Elder's question?

MR. STIEGMAN: Yeah. So I guess when Oscar Yeh was up here, we said it would be two parts, one talking about the characterization testing for the IDE or to get into the -- to initiate the study and then follow-up testing requested by the FDA. We were about to talk about the follow-up testing and then there was a new question. If he's satisfied with --

DR. RAO: Well, I think it may have been in response to Dr. Smith's question, is the feeling I get, so I'm just going to ask Dr. Smith to elaborate.

DR. SMITH: I could simplify my question down to one. My main concern was after everything was said and done, it seemed like, in clinical use, the predominant failure mechanism was at the blocker/anchor interface. And then in reading through the mechanical testing data, not the slide you showed but the one where they actually tried to make it fail, there is what you labeled as the occlusion component detachment, and in that test there was 50,000 cycles, and I was wondering if there's any additional testing with more cycles, because it seems that that was the mechanism where clinically it failed the most, but the test to test the failure was only really 10 days of cycles in human life.

MR. STIEGMAN: Right. So in discussions with the FDA, they asked us to try to

recreate those failures, and that was our objective after we got the major deficiency letter. And Ryan Siskey can describe that testing.

MR. SISKEY: Ryan Siskey, a principal with Exponent.

So to answer that question, it really is a multipart question. Oscar Yeh already presented the pre-clinical testing, which is true pre-clinical testing where they evaluated a failure mode to assess how well the anchor component and mesh component stay together under simulated use cycles, and that test was conducted up to 10 million cycles. Now, from the clinical trial, the Sponsor learned some things, and the detachment mode of failure is something that we then further investigated and developed testing to assess. Can you pull up PT-27, actually?

So this is the test or a picture of the test that was conceived of once we had the clinical failure mode where we actually directly applied loads and forces, both in a medial manner and a posterior manner, to the mesh to get it to detach from the anchor. To your point, we absolutely saw failures in the fifty or tens of thousands of cycles, relatively short-duration tests. However, what was observed was that under those loads that were applied, we could get ductile tensile rupture of the fiber mesh consistent with what we actually observed on the retrieved components. The other hat that I wear for the Sponsor is to actually assess and evaluate the retrieval devices.

And so the main thing here was to basically recreate that failure mode on the bench, and we were able to do that in a relatively short number of cycles under what would be considered relatively high loads to what the device might experience in vivo.

DR. RAO: Is that satisfactory, Dr. Smith?

DR. SMITH: Yes, thank you.

MR. SISKEY: Thank you.

DR. RAO: Dr. Elder, if you could just repeat your question.

DR. ELDER: Sure. My question was, in terms of your definition of reherniation, you said that the surgeon can identify that it was just residual nucleus material, and I was wondering how that would be differentiated from recurrent nucleus material, and kind of going back to Dr. Finnegan's comment from earlier about how you would differentiate a recurrent herniation from a disc that was incompletely resected.

MR. STIEGMAN: Sure. To answer this, I would like to call up Dr. Bouma.

DR. BOUMA: Gerrit Bouma.

You're completely right in a point that it's impossible for a surgeon, during operation, to determine if a herniation that he finds, whether there's residual or recurrent. I should point to the fact that in this study there were only two instances where this was the case, that the surgeon labeled the herniation that he found as residual. And if we would consider this as recurrent herniation, it would not change the conclusion of the study at all.

DR. RAO: Thank you.

Dr. Donshik.

DR. DONSHIK: We still really haven't heard much about the device failures. I had asked you about whether or not there was any correlation between experience of the surgeon. And then the other thing is, actually, looking at the data again, I mean, there are 32 failures in 24 months, regardless of whether or not they're symptomatic. I mean, that's 13%. We don't really have a better root cause other than fracture or migration failure. I think it would be helpful, I don't know if the data exists, but, you know, a more itemized list of exactly what happened in those failures.

MR. STIEGMAN: Sure. And I think that's an important question. Dr. Smith brought similar types of concerns up. First, to answer your first question regarding, sort of, a learning curve type assessment, we did look at the first four patients versus the remainder.

We didn't see any difference in outcomes. Hopefully that answers your question. I think the training program in place was robust. All of the surgeons were experienced, and if they weren't, there's a no train/no use policy, so they were all trained and went through cadaver training and such.

DR. RAO: Dr. Subhawong -- yeah, go ahead.

MR. STIEGMAN: I was going to start answering his second question.

DR. RAO: Sure, go ahead.

MR. STIEGMAN: Okay, so this is a lot longer of a response because I do want to make sure it's clear on the -- regarding device integrity observations. So, you know, in general, we show the table with the 32 at 2 years, and this particular chart does address out to 5 years, all available data out to 5 years, and breaks it down into those various categories. To really break down each individual type patient, I'll call up Oscar Yeh again.

DR. RAO: You are working on those axial MRI images while we're getting the rest of this stuff?

DR. YEH: Yes.

DR. RAO: Thank you, thank you.

DR. YEH: I believe DI-20 is the illustration device integrity, just to start us, because I think you asked some very good questions. I think the root cause ultimately is exactly what we're trying to address. So this is nucleus pressure. This is nucleus trying to escape the disc, and so that, in general, is what's causing all of these types of failures.

Going back to the definition, when we talk about just a migration, it's some portion of the occlusion component is now outside the disc, so beyond the posterior margin of the disc. And in this picture here, you can see that the mesh is out, but it's still attached. So I want to draw the differentiation between migration, you know, again, it's a radiographic definition of it, and sort of what's free.

And so if we can get CO-65 to go back to get that breakdown. And so focusing on the occlusion component, if it says migration only, then it's still attached, and so that's two-thirds of them, two-thirds are still attached. You also have three -- you had referenced the 32, so I'm talking about the 2-year numbers. The three with detachment only, the fact that it hasn't migrated means that that's yet another one of these situations -- categories where the mesh can be detached, but it's within the disc space, so now it hasn't gone to the epidural space. And then we're left with the six that are both detached and migrated, so this would be outside the disc space. So that's trying to give some detail on why so many of those were asymptomatic. Again, the root cause is the nuclear pressure.

If we want to walk through -- again, back to the pie chart, CO-66. You know, we did have -- you know, of the 48 that we've observed, 21 were asymptomatic. You've seen the data that Dr. Bouma presented from our trial, that Barricaid can reduce symptomatic reherniations, but it can't eliminate it. So when these reherniations occur, that nucleus sometimes displaces the occlusion component. And so we saw 19 of these, actually, observed with that, and all of the data and the differential between Barricaid and control, that's all being accounted for there. I know there's been questions about, you know, do you add more device integrity risks? That differential in symptomatic reherniation incorporates these occurring with device integrity observations.

And then we have the eight with, you know, what we're terming the standalone symptoms. Three of those were reoperated. Three of those had serious adverse events. One was a neurologic deterioration that was actually observed and continued even after the mesh migration, and one of those was a mesh migration in a patient that had never reached their ODI MCID even after the initial surgery. So that hopefully gives you some additional color on what's going on there.

You know, we've done very careful analysis doing some Cox regressions to try to see

what of these intraoperative and baseline things might correlate. So we took 20 different variables, and in the end, we just saw a couple things. You know, one was selecting the correct implant size, right? You want that mesh width to be at least as wide as your annular defect. And the second was really tall discs, and I think, again, in some of the conversation with Dr. Smith about, sort of, the occlusion component being rocked back and forth, if your disc height is particularly tall, then you're getting less support for that occlusion component. So these were the things we saw. These are the things that I think, you know, we have thought about and considered of, you know, what can we do if we had more careful training, if we were to -- we have a posterior disc height exclusion, it has to be tall enough so that we can actually implant it, but do we need perhaps something on the other side?

These are all things we've been thinking about, and sort of the net result of that is, you know, now we're showing this in Kaplan-Meier rates, but you know, device integrity rates, radiographic only, which is the blue curve; the orange curve, which are the ones that were actually symptomatic in some way, and again, there's some crossover there with symptomatic reherniations. And then getting to the green, which is -- you know, if we were to just -- as an exercise, we exclude those patients with the tallest disc heights, if we try to get to this, you know, hypothetical situation where we had no selection mistakes, you would get to the green, which is an 8% rate through 5 years, and through 2 years, I believe that rate is, you know, only about 5%.

DR. RAO: Dr. Subhawong, you had a question?

DR. SUBHAWONG: Ty Subhawong.

I'd like to revisit the issue of the control's rate of reherniation, because it seems to me or it's still unclear to me why the rate is so high compared to the rates quoted in the literature. From what I can tell from the literature, the rate seems to be around 10%,

maybe 20% or up to 30% in high-risk groups. But if you look at Slide CO-58, it looks like a cumulative rate of reherniation is around 69% for the control group. And so my concern is that the control has been set up as kind of like a straw man that's going to be easy to show superior efficacy with the device with such a high rate of recurrent herniation.

MR. STIEGMAN: So yeah, I mean, that's -- first, you know, the rate of reherniation is indicative of what is actually in the literature for the control group. And I'll call up Dr. McGirt in a second, but also -- it's also an effect of clinical studies. You had these patients under a microscope, and you take annually CT scans and MRIs and you have all of these assessments and you always sort of get higher rates of something, whatever you're looking for, and we see that with, you know, fusion studies where everyone says, hey, I have 99% fusion rates, and then once you start applying, you know, criteria to that, then they mimic what FDA has or somebody else, those rates start to drop, and that doesn't jive with literature. We sort of see the same thing with these herniation rates, because it's an effect of a clinical study. To give more of a real-world than my impression from it, I'll call up Dr. McGirt.

DR. McGIRT: Yeah, thank you. I mean, it's an important question, right, how generalizable are these two cohorts in the study design. You're right, when you look at historical controls on all lumbar disc surgery studies to date, it's going to range anywhere from 5% to about 14%. And you referenced SPORT data, which was a well-controlled RCT. When you look at national registry data, we know about 1 in 10 patients will return to the OR in the first year. That's in real-world care in the United States, and that's the reality of the landscape we practice in here at the United States.

This is the first study, however, that studies in a controlled prospective way the incidence of symptomatic recurrence in big annular defects. So, you know, when I first looked at this and digested this, my gut was wow, I don't have one in four patients coming

back to the OR. But to be fair to the trial design, it wasn't even established to measure all of Matt McGirt's discectomy patients. It actually was targeting a high-risk population with large defect. I mean, I think we have some slides. I've done a meta-analysis, and there have been other studies on one of the slides shown earlier, where we do know in large defect retrospective reviews and some single-surgeon prospective reviews, that large defect incidence does approach over 20-some percent. So we already find ourselves in an interesting situation where this is a novel study, in that it's the first well-designed study to look at, you know, what is the re-incidence -- what is the recurrent incidence in greater than 6 mm or a big hole?

So I don't think there's a historical precedent that makes me disbelieve this. If there was a hole or a challenge in how we were measuring this endpoint-wise, I might question it more, but I think it's a solid study design, the endpoints are objective, MRI validated and adjudicated, and there's no historical precedent to suggest this is erroneous.

DR. RAO: Dr. Sayeed had a question and then Dr. Katz.

DR. SAYEED: Was there any comparative analysis between the width of the device and, one, biomechanically and, two, in terms of increased pressure which may, you know, cause reherniation? So I guess my question is really a two-part question. Was there biomechanical testing done between differences in width? So the 8, 10, and 12? And then was there any correlation with reherniation rates? I didn't see that teased out in the study design.

MR. STIEGMAN: Sure. I'd like to call up Oscar Yeh to address that.

DR. YEH: The testing that I described earlier was performed on the largest sizes, so the 10 mm size and 12 mm size being thought of it as a worst case. We didn't see a difference between the size of the implant and reherniation rates. You also need to consider the annular defect with it. So, for example, if you had a 6 mm wide defect but you

implanted an 8 mm wide device, you know, that may not be the same as a 10 mm in a 10 mm. But even when striating it that way, you know, we call that the overlap, we didn't see a difference in the reherniation results.

DR. RAO: Dr. Katz.

DR. KATZ: Lee Katz.

I'm going to go back to the baboons again, if you don't mind. Actually, if you could put up the FDA Slide Number 9, if that's possible. Right. So here's the FDA Slide Number 9, which is from the baboon study, which actually shows the osteolysis and several of the Barricaid implants, and I'm wondering if your pathologist could maybe explain, in a little bit of detail, the findings we see here, and do you have cross-sectional histology going through, which would be almost as good as the MRI essentially, to try to understand the F, which we see in the top vertebral body, which is labeled L4, and we see it in the superior endplate of L6. So that would help us a little bit to understand a little bit about what that material is that's actually causing the osteolysis.

MR. STIEGMAN: Sure. So yeah, I'll call up Dr. Lalor. But just to give -- she was only asked to review these. Alizée and the pathologist that did this is not here, and Alizée actually doesn't exist anymore. But she was asked to review this and give her impression, so I wanted to provide --

DR. KATZ: Do you have any cross-sectional imaging through actually the areas of lysis? That would really be helpful. I don't know if you have that. Or are these the only two pathology from the baboon study?

MR. STIEGMAN: While we're looking at the MRI, we'll see if we have that as well.

DR. KATZ: Okay, thank you.

DR. LALOR: Yes, Peggy Lalor from Histion in Everett, Washington.

I did have an opportunity to have a quick peek at the baboon slides. I did not do a

full evaluation. There were some difficulties with the slides when I did take a look at them. And one thing with ground sections, ground sections can be done two ways. The way we do them in our facility is we grind them down to less than 100 microns, and we stain them with a stain that's different than this stain and actually stains better to enable us to see both bone and the soft tissues, and then we cover-slip them, and that seals in the stain and the results. The sections that I was given had been reviewed by several pathologists, and by the time I got them, they were in a different stage. They were not cover-slipped ever. So when a pathologist reviews a ground section that hasn't been cover-slipped, what they typically do is put glycerin on it, put a cover slip on it, and then the stain tends to leach away. So the more you look at them, the less you can see.

So, however, having said all of that, you can see that what I was looking at was less than perfect, but my impression was that yes, there were some areas around the device that did have some evidence that there were some particles president -- present, excuse me. And again, consistent with my findings in the retrievals from the human study, I didn't see any evidence of scalloping, which means no evidence of active osteolysis. And that's really all I could tell from these slides.

DR. KATZ: Um-hum. I just think it's interesting, and you can correct me and so can the Sponsor, but if you take a look at L6, it seems to be that the device is off center, right? It looks like it's to the right; is that correct? And it's interesting that the area of osteolysis is central, and I'm still trying to understand what would be causing that fibrosis, which I think was mentioned before correctly, that there's the -- because it looks like F, by the way, there's an F there -- I think that stands for fibrosis -- within the superior portion of the vertebral body on Number 6, and there's an F involving the inferior endplate of vertebral body Number 4. So there's, I think, the -- I'm just trying to understand what's causing that reaction and if that's fibrosis. Well, it looks like it is. I just didn't know if you had slides that

would confirm that.

DR. LALOR: I do not have anything that --

DR. KATZ: Thank you very much.

MR. STIEGMAN: And I will provide my response. I think it's generally because of the size mismatch. You know, the occlusion component is laying flat in that disc space, and whether it's straight or curved a little bit, that's where you see it. So it's maybe not indicative of where the anchor symbol is.

DR. WEISBRODE: May I comment on those images a little bit?

DR. RAO: Sure.

DR. WEISBRODE: If you could put those images back on. To me, the astounding feature about these images is the sharp demarcation line between normal and abnormal. To me, this is not the appearance that I see in mechanical use, which is more of a regional effect. And it also clearly isn't the effect of a more systemic intradisc inflammatory mediator. This is a focal -- it almost looks like a mechanical bite out of that thing, and I think, in the earlier images in the baboon, I think there's amazing shots of mesh immediately adjacent to endplate with cartilaginous endplate lysis with the best that I could see without significant inflammation, but that was very difficult to determine. And without fibrosis.

I don't think it really relates to the safety factors, but I'm intrigued with how this mesh does this. And I almost equated some of this fibrous connective tissue, similar to pannus that we can see, and many of you know pannus is associated with inflammatory -- sterile inflammatory diseases of the joint, but pannus can sometimes be amazingly cellular free, and the fibrous connective tissue in the pannus is able to express cytokines, including -- which can bring in osteoclasts themselves. So it's possible that the fibrosis alone is a significant primary event. Not to say that there isn't an inflammatory response secondary

to the material as well.

DR. RAO: Thank you.

Dr. Finnegan.

DR. FINNEGAN: So just to follow up on that. One of my questions had been do you guys know how much BPA there is in your Dacron and have you done serum levels, because that may actually explain some of this.

MR. STIEGMAN: Yes. Yes, I apologize. Some of these pages just stick together, and I saw that response and was going to get to it. The BPA question -- if it will just come up on my -- so testing of the material was in accordance with ISO 10993-18, using both polar and non-polar extracts, and no BP was identified. BPA, sorry.

DR. RAO: Thank you. If we could see those axial MRI images, please? We're running out of time.

MR. STIEGMAN: Sure.

DR. FINNEGAN: Dr. Rao, can I ask a question while we're waiting?

DR. RAO: Sure.

DR. FINNEGAN: What do you think the effect of not blinding is on your controls?

MR. STIEGMAN: The effect. I mean, there was a small population that was blinded, and we saw no effect on that population compared to Barricaid, or both those populations compared to the unblinded population. So we saw no effect.

DR. RAO: Okay, if it's going to take some time, why don't we take our break right now, and then we give you 2 or 3 minutes after we come back from the break to pull it. Would that work for you?

MR. STIEGMAN: I think so. Thank you very much.

DR. RAO: Okay. Why don't we take a break now for 15 minutes, and we'll meet back here at 3:20 sharp. Again, please don't talk to anyone about the contents of the Panel

meeting or the subject of the Panel meeting. And we'll see you back here soon.

(Off the record at 3:06 p.m.)

(On the record at 3:20 p.m.)

DR. RAO: We're still waiting for Dr. Elder, I take it. Okay, it's 3:20. We're going to get to the questions in just 2 minutes, but I'm going to let you just complete the axial MRI images, if you don't mind.

MR. STIEGMAN: Yeah, thank you. I'd like to call up Dr. Mark Schweitzer to review this.

DR. SCHWEITZER: So we have two MR images for you. Sorry it took so long to get them. So this is a recurrent disc herniation, right sided, in a Barricaid patient, asymptomatic disc herniation described by the core lab. I'll give you a second to digest that. And then I'll show you a baboon for Dr. Katz.

DR. RAO: Could you point out exactly where the disc herniation is, please, versus no root?

DR. SCHWEITZER: I don't know how I can do that.

DR. RAO: Is there a mouse or -- Dr. Katz, do you have any thoughts on that? Do you have any thoughts on that?

DR. SCHWEITZER: Again, it's very hard to see in a bright room. You guys have a mouse, and I don't.

(Laughter.)

(Off microphone discussion.)

DR. SCHWEITZER: I'm going to put the arrow on it and then go back to the microphone.

DR. RAO: Um-hum.

DR. SCHWEITZER: And that is the disc herniation; it's displacing, as far as I can see,

the nerve root somewhat centrally, independently read by the core lab. I'm just pulling up what the core lab described.

DR. RAO: Do you agree?

DR. SCHWEITZER: We had a few minutes to get -- there were other images in the series that were convincing.

DR. RAO: Okay. Okay, let's see the other image.

DR. SCHWEITZER: The other image is the baboon, so there's kind of a sagittal oblique image and this is -- and there's two Barricaids in the baboon and a control level above it and I just -- because, by request, you wanted to see what the MR looked like, and again, very hard on just one or two images to look like -- but it does look like the material in the baboon that's going into that lytic defect is likely discal material based upon its position and signal characteristics.

DR. RAO: Dr. Wang.

DR. WANG: I was wondering, in terms of the deployment of the device, is when it's implanted, is there visual -- so it leads back to imaging as well, but is there visual confirmation that the mesh is, indeed, closing the entire annular defect, or how is that confirmed? And along those lines, do you have any earlier postoperative imaging confirming that? Can you see the mesh on MRI at all?

MR. STIEGMAN: You know, to discuss the implantation procedure and hopefully answer your question, I'll call up Dr. Kursumovic.

DR. KURSUMOVIC: Kursumovic, Adisa.

Mesh is not visible, but you have the iridium marker, which you can see, and you can see it during the fluoroscopic procedure when the mesh opens and where the mesh ends on the end of the procedure. So you do not see all the layers of the mesh, but you see this iridium marker clearly, which is located on the end of the mesh.

DR. WANG: So in terms of visualizing your defect in the annulus, you can't tell --

DR. KURSUMOVIC: Of course. The defect is already -- the defect you need to visualize first, then when you start employing the annular closure device, Barricaid, you will see the iridium marker inside of the -- and you see the defect first, then you implant the Barricaid inside of those defects.

DR. WANG: Yes. And once it's implanted, you can see the annular defect --

DR. KURSUMOVIC: Closed, yes.

DR. WANG: -- completely closed.

DR. KURSUMOVIC: You actually look underneath a microscope. You look if the proper implantation technique and the proper place is the place, yes.

DR. WANG: Okay, because you made a comment earlier that you thought some of the reherniations could be due to incomplete closure of the annulus, but would you say it's part of the surgical technique to visualize the entire annular defect?

DR. KURSUMOVIC: Well, that's probably due to the anatomical limitation that we have. You have a dura on the medial side and facet joint to the lateral side, and sometimes you have the feeling that you're having covered the whole defect, but in fact, maybe a small portion of the defect is left, like most probably medial. You need to retract around the nerve root in order to visualize this. Almost we have a good feeling that the defect is completely covered, and the idea or theoretical idea of why this reherniation may occur is that you didn't cover the last, I don't know, 1 or 2 mm of the defect.

DR. WANG: One more question. So on the reherniations with the device, then, were most of those medial, or did you look at that?

MR. STIEGMAN: I'm sorry, can you repeat the question?

DR. WANG: So if possibly the --

MR. STIEGMAN: Yes, the majority of the reherniations was located medial, some

lateral to the -- and we've even seen some contralateral reherniations.

DR. RAO: Thank you, Dr. Wang.

Any other quick questions?

(No response.)

DR. RAO: Okay, I think --

MR. STIEGMAN: If I could, just real quickly, if the Panel Chair allows, there was one point made earlier that I would like to clarify, and I know it's going to be probably a big topic of discussion after I sit down. Can I make that clarification real quick?

DR. RAO: As long as it takes a very brief period of time because we -- I don't want to kind of cut into the questions.

MR. STIEGMAN: Yeah, absolutely. So we talked about boxing annulotomies, and this is really going to Dr. Graf's concern regarding 40% created new, and I was unable to get -- really, what I was trying to get at was the created new defects in both the control and then the created new defects in the Barricaid group, and you can see the rates, that they're comparable, one, especially in the box category. So really, there's no, you know, extension of the defect to create the higher reherniation rate, by any means. And then if you look at the results, you can see that there's no differences within this group as well. I know we're under a time crunch. I'd like Dr. McGirt just to come up real quickly to talk about his experience to validate this.

DR. McGIRT: I'll keep it really quick because you asked me to, and I think it's a really good point that a couple of Panel members have brought up, is this box annulotomy phenomenon in this study group relevant to the U.S.? Does it create some artificial study population? I think it's a great question, but my belief is no. When you look at how these characterizations were defined in the study, okay, I actually flew to Brussels, met with three surgeons who did this, watched them do this to understand exactly is this representative,

do they do it differently there? And the answer was no. They are asked to, on a piece of paper at the end of the discectomy, to answer the following question: Was new annular opening created during the discectomy, okay?

So everyone here who does discectomy knows we wish they were all pieces of crab meat; you could, you know, swirl out with a nerve hook and pull out and be done. But there is a subset, you need to use a little down-going turret, you need to work a little harder, and in that process, you are creating some annular opening. In that case, which is a large subset of my discectomies, I -- and these surgeons marked yes, annular opening was created or annular defect created in some way.

A completely separate question is then asked at the end of the case: Once you size and measure that annular defect, whatever it may look like after you do your standard of care discectomy, maybe it was a small nerve hook sweep, maybe a down-going turret, maybe you had to work on the annulus a little bit, how would you characterize the geometry? Was it a slit, was it a cruciate, did it look geographically or geometrically like a box or oval? And they have to mark one of those.

So I went in saying are you guys doing TLIF box openings for all your discectomy, and that was not what I learned, that they were saying no, we have to -- we're asked if we created or widened the annulotomy in any way, however it takes us to do a good discectomy, and then how would you characterize that whole once it's done? So I was relieved to understand that when you see a 29% incidence of a geometry characterized as a box, it wasn't an 11-blade annulotomy box, and that if an annulotomy was created and marked as yes, new, they weren't going in there and doing these subtotal discectomies. It was they felt that they had to widen the annulotomy.

So because of those, and I know I ran over time there, I just wanted to make sure the Panel gets the vantage point that I got actually diving deep into that, that it is actually

similar to how we do it in the U.S. Thank you.

DR. RAO: Thank you. Well, thank you very much. Thank you to the Sponsor for outstanding responses to the questions that the Panel had.

At this time, let us focus our discussion on the FDA questions. Panel members, copies of the questions are in your folders, and they're also the last few pages of the FDA slides, so you'll find them one or the other place. We're going to have Dr. Hwang come up to show us the first question, and as the questions come up, I will go around the table and ask people for their response to these questions. I would ask that each Panel member identify himself or herself each time he or she speaks to facilitate transcription.

Dr. Hwang, could you please show us the first question?

DR. HWANG: Okay. So the Sponsor planned to enroll a study population that includes subjects with increased risk of disc reherniation (for example, large annular defects defined between 4-6 mm tall and 6-12 mm wide post-discectomy) that would potentially benefit from a permanent implant to prevent reherniation compared to a discectomy alone. After review of the data summarized in our Executive Summary, it appears that the patients were enrolled consecutively across multiple sites, and the enrolled study population appeared to differ from prior literature reports regarding the incidence of "at risk" disc herniation types as identified by Carragee (2003). For example, the Barricaid study had a much lower number of "fragment-fissure" type annular defects, which are associated with a low rate of recurrent lumbar disc herniation in the enrollment population. Additionally, the majority of the study subjects appeared to receive, I guess, these box-shaped defects during discectomy procedures prior to randomization, which suggests surgical resection of the disc annulus may have gone beyond the extent required for performing a limited discectomy as defined by the Sponsor. Based on the observations regarding the study population described above and in our Executive Summary, please comment on the following:

a. Please discuss the patient characteristics, herniation types, and size and types of annular defects that would likely benefit from an annular closure device and if that population was adequately investigated in this study; and
b. Comment on the differences noted between the limited discectomy procedures reported in the literature compared to the treatment received by those enrolled in the Barricaid study. Then, please discuss whether these differences had an effect on the clinical outcomes, especially with respect to reherniation rates and subsequent surgical interventions in the control group.

DR. RAO: So let's take Question 1a first, separately. So patient characteristics, herniation types, and size and types of the annular defects that would likely benefit from an annular closure device and if that population was adequately investigated in the study.

So anyone around the table? Dr. Graf.

DR. GRAF: This gets back to exactly what my initial question was and my overall concern that there was a 39% created annular defect, which, by definition of the study to be included, was 4 to 6 mm by 6 to 12 mm, which in my mind is quite a large defect that was created. That's why I feel that in this study the rate of recurrent disc herniations for the control group might be unintentionally elevated as compared to what we see in the literature.

DR. RAO: Dr. Wang, you look like you want to say something.

DR. WANG: Do you want us to comment on each?

DR. RAO: No, just Question 1a first.

DR. WANG: Just the one?

DR. RAO: Yeah.

DR. WANG: Yes, I would say that adults, average age 43 with a large annular defect, with this study, was adequately investigated and would likely benefit according to this data.

DR. RAO: Okay.

Dr. Finnegan.

DR. FINNEGAN: So I'd like to address patient characteristics. This is Maureen Finnegan. There are a couple things. If you look at their data, the BMI for most of their patients ran between 25 and 26, which is a different patient population than a lot of the disc problems that we see.

Secondly, their disease age ran from -- young to 75, those are different diseases for each of those age groups, and they didn't really stratisify them and -- stratisfy? Strat -- whatever. Separate them into groups. And statistically, and I'm no more of a statistician than our bioengineer, but you need very large numbers of patients in each of those groups in order to be able to say whether there's a difference or not.

And then the last point was that 44% of their patients are currently smoking, which probably has some effect on the annular function postop, anyway, so I think there's a problem with their patient characteristics.

DR. RAO: Thank you.

Dr. Sayeed.

DR. SAYEED: Dr. Yusef Sayeed.

I agree with Dr. Finnegan. I think some of the things that we should address in any trial of a medical device that's potentially going to market is patient demographics; we should look at age, sex, gender, and really risk stratify, not just based on younger than 43 and older than 43. To me, that's just poor, poor design. But instead, really look at, you know -- you know, definitive age range as, you know, degenerative -- degenerative processes occur in the 40s and begin accumulating over that period of time. So we should treat those age ranges and stratify them accordingly.

In terms of one thing that we didn't discuss at all is race and ethnic differences

between treatment types, which really never gets brought up at any FDA meeting, but it's something that we, at least, should be looking at.

In terms of size and types of the annular defects, I concur with my colleagues, that it is concerning that this box annulotomy takes place before device implantation and then this pretty significant reherniation rate.

DR. RAO: Thank you.

Any other questions with respect to Question 1a? Whether we've got a population --

DR. KIM: Can -- yeah.

DR. RAO: -- that's representative and it's been adequately --

DR. KIM: Just about the surgical procedure, the size of an annulotomy. As a surgeon, when you do open up the annular, we use instruments to remove disc -- the size. The instrument is around 4 to 5 mm. So 4 to 6 mm, this is not a size. I think, when we do surgery, we see this quite often, I believe.

DR. RAO: Okay. Dr. Melkerson, with regards to Question 1a, the Panel generally believes that there are some limitations with the patient group that was investigated in terms of we may not have all the answers we want with respect to the different age groups and other stratification that we could carry out within the patient population, but that in general, in terms of the size of the annular defect, the patient population was appropriately representative of the type of people that we see, and the device was adequately investigated in terms of the annular defect. Is that adequate?

MR. MELKERSON: Yes, that's adequate.

DR. RAO: Thank you.

Let's move to Question 1b. Please comment on the differences between the limited discectomy procedures reported in the literature compared to the treatment received by those in the Barricaid study, and then discuss whether these differences had any effect on

the clinical outcomes, especially with respect to reherniation and subsequent surgical interventions in the -- Dr. Baron.

DR. BARON: Yeah, I think this study --

DR. RAO: If you could just turn the microphone on.

DR. BARON: Oh. I think this study is novel in the sense that they were really looking at the disc at so many endpoints of time with so many modalities, you can't possibly use those historical controls when they didn't have this level of radiologic scrutiny as a basis for a baseline level of recurrent herniation.

DR. RAO: Not? Could you just --

DR. BARON: You could not use the historical controls. I mean, these guys here are looking at repeat MRIs, repeat CT. These are studies that you would never get in clinical practice. So their meaning of a recurrence is highly, highly sensitive.

DR. RAO: Okay, thank you.

Dr. Subhawong.

DR. SUBHAWONG: Ty Subhawong.

Just to echo that point, also, the historical controls, the MRI scanners technology has greatly improved in the past, you know, 10 to 15 years, so you would expect, perhaps, more sensitivity in detection of higher rates of reherniation with newer-generation scanners that just have higher spatial-to-noise or signal-to-noise resolution and higher spatial resolution.

DR. RAO: Dr. Smith.

DR. SMITH: I similarly echo those comments. If there was a bias error or a higher incidence, it was sort of systemically across both treatment arms, and so I think -- I don't think it would've affected the overall comparison between the cohorts. And I agree with the other comments that if there was a higher incidence, the higher rate of imaging likely could have resulted in that.

DR. RAO: Dr. Wang.

DR. WANG: So I was just going to comment. I think in terms of the description of the discectomy versus what's in the literature, it does seem, on paper, that the annulotomies were really quite larger than what we might expect from the literature, and in that regard, I think I'm just needing to rely on what Dr. McGirt says about observing these discectomies in a different outside-the-U.S. population. So it seems that there's some differences, but the observership, maybe, is better than what is documented.

DR. RAO: Dr. Elder.

DR. ELDER: I think, in terms of the limited discectomy in the literature versus what was performed, I think there's some challenge here in interpreting it, but I do think they're addressing the highest-risk population. Whether you come in and have a large defect, that patient is going to be at high risk of herniation, or else at the end of your procedure, actually it will lead to compression if you're left with a large annulotomy; that seems like the patient who would benefit here.

DR. RAO: Dr. Melkerson, with regards to Question 1b, the question relates to whether the limited discectomy procedure reported in the literature compares to those received in the Barricaid study. I think the Panel generally feels that we're limited, to some degree, by the fact that there may be some discrepancy between what's described in the handed-out material as a creation of a box annulotomy versus what has been reported at the Panel meeting as perhaps just an extension of a normal slit annulotomy procedure so that, given that lack of clarity and that lack of certainty, in general, the operations seem roughly similar to what are normally carried out for disc removal procedures. I hope that's adequate.

DR. HWANG: So as a follow-up, is -- would you say that -- so I know that originally we discussed all of the annulotomies as created -- the box annulotomies as created, but

given the size descriptions, would you say that those are as accurate as well to what you guys observe in practice?

DR. RAO: You know, I think that's -- my personal opinion is that it's difficult to be certain about because you put a device in to measure the width of the annulotomy, or you put a device in to measure the height of the annulotomy, and that device has its own -- it's a solid object. So I could kind of put in a device that gets even wider and wider, so you can keep creating an increased size of the defect. And there's not been a discussion on that part of the defect measurement part of the operation, and I don't want to get into that part right now. So it's difficult to be certain, but overall the operations, as described, seem roughly similar to what is routinely done for a disc removal procedure.

And I'd like to invite the Panel members to see if they have anything else to contribute to that because I don't want to go back to either the FDA or the Sponsor at this point. Generally agree, everyone? So I think that's -- Dr. Melkerson, is that adequate?

MR. MELKERSON: Yes, thank you.

DR. RAO: Thank you.

We can move to Question 2.

DR. HWANG: The Sponsor reported 40% of control patients with an endplate lesion compared to 88% of Barricaid patients. Furthermore, the control patients with EPLs have lesions that are smaller and appear to stabilize sooner and present features more in line with Schmorl's nodes. In contrast, the EPLs of Barricaid patients are larger than those of the control, progress in size faster, and have radiographically distinct features and show signs of mesh subsidence into the lesion. However, based on secondary analysis performed by the Sponsor, there does not appear to be a correlation with the presence of EPLs and measured clinical study outcomes. Based on the observations regarding EPLs highlighted in the Executive Summaries, please address the following:

a. Please comment on any present and future clinical impact or relevance of the EPLs; and

b. Please comment on any additional analyses, including what time points that should be conducted to evaluate the clinical significance of these EPLs.

DR. RAO: Thank you.

Let's go to Question 2a, so the presence -- comment on any present and future -- the clinical impact of these endplate lesions. Or endplate changes, as the Sponsor called them. So presence and future significance --

DR. WEISBRODE: Actually, I have a question. Would there be concern about secondary effect -- the effect of osteopenia, let's say, postmenopausal osteoporosis, not osteopenia, but true osteoporosis? Could these defects be of concern if one of these individuals comes down with significant postmenopausal osteoporosis?

DR. RAO: Dr. Katz.

DR. KATZ: I think, as a radiologist, you know, when we see a lytic or a lucency or a hole, you know, our concern is whether this is something that's cystic or something that's solid. So I think that it's pretty clear that it's not cystic and that it's solid, and I think that the MR as well as the pathology has shown that it's fibrotic. So I think what we're talking about here is, you know, sort of a foreign body reaction of some type that seems to be, you know, in certain cases, continuing to grow. So I think that we don't really know what's causing it. It may be from the mesh, it may not be. So the question is, you know, what's the impact? I think it's tough for me to come down to it, although I press them, you know.

But I think, in terms of Dr. Weisbrode's comment, that, you know, even though in a young adult, a fibrotic lesion is probably not going to cause a huge clinical impact, but if it was an older person, say an older woman who had osteoporosis and they continue to extend into the bone, there may be some relevance, I think, in the future. So I think that

the thing for me that's confusing is that I don't understand what's causing it unless it's related to the mesh and this is sort of a foreign body reaction to that material.

DR. SUBHAWONG: Ty Subhawong.

Along the same lines, I agree with Dr. Katz. We often see things in radiology where the clinical correlation with the radiological findings aren't always straightforward. The one issue that was addressed that I had was whether there were increased or whether there was an amount of increased bone marrow edema pattern with these lesions. Oftentimes bone marrow edema is associated with pain, and specifically, one is associated with endplates, it can be associated with low back pain, and that didn't seem to be the case with these lesions.

So it seems like the Sponsor did a pretty thorough investigation looking into what the clinical ramifications of these findings were, and it doesn't seem like there are very strong correlations with pain or with device failure.

DR. RAO: Dr. Donshik.

DR. DONSHIK: With respect to the lesions, it does look like the Sponsor attempted to quantify and states that the largest lesion was less than 8% of vertebral body volume and then goes on to say that, really, unless we're at 50% or more, we shouldn't -- paraphrasing, we shouldn't be concerned about structural integrity. So I agree that perhaps osteopenia, osteoporosis, may alter that dynamic somewhat. To what extent, I don't think any of us know.

And then the other thing is, though, in general, disc herniations and surgery, at least in my practice, are not in osteopenic and osteoporotic patients, generally, but usually younger folks who are less likely to be osteopenic and osteoporotic.

DR. RAO: Thank you.

Dr. Sayeed.

DR. SAYEED: I do have some -- I'm Dr. Yusef Sayeed. I do have some concerns about these lytic lesions. The Sponsor really only provided two histological slides that -- you know, where those slides were taken is questionable to me. I think those are probably at the anchor site versus at the mesh site.

The second thing is, you know, in terms of MRI findings, there was only two examples that, you know, they really produced. As we all know, case series doesn't make evidence; instead, we really need to look at real large, large multi-institutional trials, and at this point, you know, I honestly can't say that this device is safe just based on two examples of each. So, you know, I think that our job, as Advisory Panel members, is to really weigh the evidence and determine if a device is safe and efficacious, and I certainly don't think that the Sponsors were able to show that today.

DR. RAO: Dr. Wang.

DR. WANG: I was just going to comment, also, that I also think there's some potential future impact on this. Although the numbers were small, I think the data about when these lesions stabilize is not that clear in the Barricaid group and also looked like a greater number went on to fusion, and this is a young population who will have future impact if they go on to early fusion.

DR. RAO: Thank you, Dr. Wang.

Dr. Evans.

DR. EVANS: I did have some concerns about what we know about the effect long term. You know, the primary outcomes were conducted and analyzed on mITT completers, which really isn't mITT; they lose about 9% by the time you hit Week 24, and there's a little bit more loss in Barricaid than there is in control and thus may not be exactly random.

Now, for the efficacy analysis, the primary endpoints, the co-primary endpoint analysis, the magnitude of the effect seems large enough that it's fairly robust no matter

what happens there. But when you hit the safety, particularly long term, you know, Dr. Polanon (ph.) made a comment about long-term effects in her comments, and by Year 3 the numbers are fairly dwindled in such that you'd be concerned that censoring, you may be censoring patients who are either more or less likely to have these lesions, and by Year 4 you've lost 50% of the patients.

So the question is what are you unable to see from patients due to lost to follow-up or dwindling over time, and what are the consequences, you know, regarding lesions, and what are the consequences of those lesions a couple of years down the road?

DR. RAO: Thank you, Dr. Evans.

Yes.

MS. SCHWARTZOTT: I'm looking at this from a patient perspective, and as much as I want to heal my back pain, I really question the long-term effects of this. I'm wondering if they should be looking at other materials for the mesh, but I think we really need to study, long term, what are the lasting effects of these lesions.

DR. RAO: Thank you.

Yes, Ms. Starowicz.

MS. STAROWICZ: This is Sharon Starowicz.

Again, just to Jennifer's point, just to remind the Panel again, it's very rare in spine and orthopedic studies to see such a substantial number of patients followed out to 5 years. So I think I would just ask the consideration of the Panel to look at that and look at the volume and extent of information and data that's been presented, particularly relative to the threshold of reasonable assurance of safety and effectiveness.

DR. RAO: Thank you.

Dr. Smith.

DR. SMITH: The comment I would make, I think, from the data presented today, it's

pretty clear, at least out to the 5-year follow-up, that these lesions weren't causing a problem, but I also think it's clear from discussions that we don't really have a consensus on what the lesions represent. And so I think, from a safety perspective, within the data presented, it doesn't appear they're causing a problem, but we don't really know what they are. And so to Part 2b, there probably could be some work in terms of additional analyses just to elucidate the nature of these lesions and if, perhaps, for patients to have them if they require longer-term follow-up.

DR. RAO: Thank you, Dr. Smith.

Dr. Elder.

DR. ELDER: Just to piggyback on Dr. Smith's comments. Although I think it's hard to say that these aren't causing any problems after 5 years, since there's only 20 or 25% of the patients that have data out to that point, so I think we can really only say definitively at around 2 years that there's maybe 3 years that they don't seem to have an effect. But this is a young population, predominately in their 40s and 50s, it looks like, in the study.

DR. RAO: Thank you, Dr. Elder.

DR. WEISBRODE: I think, very important, that the Sponsors presented was the sclerotic margins and the lack of growth at the 5-year period, and we compared that to the baboons, when the baboons had minimal sclerotic reaction, correlates well with the suspicion that the size of the mesh was causing the more progressive lesions, because at the end of the 3-year study in the baboons, the lesions were still enlarging, as where that was not the case in the human situation to 5 years out. I'm impressed, in fact, that they have a sclerotic margin at the 5-year period.

DR. RAO: Thank you, Dr. Weisbrode.

Dr. Melkerson, with regards to Question 2a, I think the Panel generally feels that these endplate lesions or changes have some significance. I think the Sponsors have shown

nicely that they do not appear to have much clinical effect over the course of the follow-up, but there are still some concerns that the Panel has, and the concerns are based on the fact that, Number 1, we don't know exactly what these radiographic lesions represent on a histological basis. Number 2, we don't know the impact of these lesions in bone that may not have normal mineralization. Number 3, we don't have histological answers to exactly what this lesion is going to do long term, either in terms of an inflammatory or fibrotic response. Number 4, we have some concerns because the statistical methodology used through some attrition of data may not be giving us all the answers that we'd like to have.

Is that adequate?

MR. MELKERSON: Yes, thank you.

DR. RAO: Thank you.

Let's move on to Question 2 -- we still have 2b. If we could go back to that last slide. We didn't respond to Question 2b. So now we want to talk about what additional analyses, for example, what types of assessment at what time points, should be conducted to evaluate the significance of these changes.

Dr. Gilbert.

DR. GILBERT: So as I understand this, there's a 1-year window where this device provides a benefit, that you reduce the number of reherniations, but only in half, so there's essentially 50% that continue to occur, and I don't see any information about why. I mean, there's discussion, sort of assertion really, that there are these inadequate margins or other factors. There may be a fundamental design flaw in the device that just precludes an ability to stop herniation, say, at the bottom of the device. And so I think some exploration of that cadre of patients that see reherniation with the Barricaid, what that root cause of reherniation is, I think that's going to be very critical.

And then the other comment I would have is, you know, we're doing this 1-year

benefit and then wondering about 40 years of safety and what goes on for that 40-some-odd-year-old person through the rest of their life or 20-some-odd-year-old person to the rest of their life, and that's a really hard thing to predict, right? There's so many ways that it can affect it, but more than a 2-year assessment of the safety or even a 5-year assessment of the safety is needed to really understand. If there had been no endplate lesions that are associated with the Barricaid device, I would be less concerned. The fact that there are means that we need to follow -- they need to follow the progression of this or lack of progression out beyond -- well, beyond 5 years to assure safety.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Finnegan.

DR. FINNEGAN: A question for radiology colleagues. My radiology colleagues are always talking about their newest toys, and it's my understanding there are some MRIs now that can do cellular-level sodium phosphate, etc. Would this help in delineating what's in there?

DR. RAO: Dr. Katz, Dr. Subhawong?

DR. KATZ: I would say no. Short answer. I don't think that's going to give you the answer of what's in there.

DR. SUBHAWONG: Ty Subhawong.

Yeah, I think those types of machines are probably still in the investigative stage right now. I think most of the useful information we can get from an MRI on this sort of implant would be morphological, and I think that, you know, using high-field strength MRI is probably adequate to address most of the questions that we would have in terms of implant integrity and reherniation rates.

DR. RAO: Dr. Finnegan, the grass is not greener on the other side. They're just as outdated as we are in all fields.

(Laughter.)

DR. KATZ: I think the only other thing is, you know, of course, the question of giving contrast, you know, if you think this is an inflammatory response, maybe there's a subset of patients following surgery and looking to see, in fact, if where this inflammation is beginning, you know, is it really beginning around, you know, the mesh? Is it beginning away -- I mean, there's just a lot of questions right now that I don't think I can answer, but I think that in the future, potentially, the consideration of giving intravenous gadolinium during the study would be helpful.

DR. RAO: Thank you, Dr. Katz.

Any other additional analyses, and maybe at what time point should be done to assess these EPL/EPCs? Yes, Dr. Sayeed.

DR. SAYEED: I would recommend at least a 10-year follow-up, you know, that -- at least then you can see, you know, a decade's worth of data and help to better characterize what these lytic lesions are. In addition, you know, what we don't want to happen is another silicone breast implant. That would be the worst-case scenario.

DR. RAO: Did I see a question? Ms. Schwartzott? No.

Dr. Smith.

DR. SMITH: A comment I would make is I think it's hard to recommend definitive follow-up points when we don't yet understand the lesions because the control group also had lesions. They referenced Will Weiner's paper from 2015, and just doing surgical intervention to the disc space does cause endplate lesions. We believe, I think, consensus is that some of these lesions are distinctly different and are due to the implant, but we don't really understand what they are, and so I just don't see how we can make a cogent recommendation for how to clinically follow them at this time.

DR. RAO: Thank you, Dr. Smith.

Dr. Elder and then Dr. Gilbert.

DR. ELDER: I mean, I think I would like to see more complete data out to 5 years, and if that shows stabilization of everything, including in the control group, I think that may be adequate, but if there are still concerns, I think it could definitely -- should definitely extend out further, perhaps out to 10 years. Additionally, as part of that, I think the Sponsor should look at not just which patient is going to get fusion, but the actual pseudarthrosis rates between the two groups, if they have lesions, and if they don't have lesions, to see if that does complicate any revision surgery.

DR. RAO: Thank you.

Dr. Gilbert.

DR. GILBERT: I don't know if this is possible, but -- so two thoughts. One, postmortem retrieval and analysis of these lesions as one potential follow-up, and the second would be biopsy at the point of, say, fusion or other instrument, you know, of that segment. Could you take a histological sample for evaluation at that point?

DR. RAO: Okay. Dr. Melkerson, with respect to Question 2b, in terms of additional analyses that may help us understand these EPL/EPCs, I think the Panel generally feels that some additional analysis is important. The Panel is not entirely sure on exactly what the best analyses may be because we're a little hindered by the fact that we don't exactly understand what the lesions constitute at this time. However, some suggestions are that we use MRI IV contrast on future patient sets to understand what the local inflammatory or other response may be.

Number 2, obtain some type of additional histological sampling, either postmortem or intraoperative at the time of subsequent operations. And my thought is also that we should maybe try and analyze how many of these are going on to spontaneous stabilization/fusion with development of heterotopic ossification behind the implants

because it's my suspicion that those are the ones that go on to do slightly better. So I think an analysis of ossification, posterior or adjacent to the implant, and correlation of that ossification with the lesions might help us understand the implant a little bit better.

And there's some thought amongst the Panel that we do need longer-term follow-up to better understand these lesions, and I'll leave that to you to decide whether that should be 5 years or a bit longer. Is that adequate?

MR. MELKERSON: Yes, thank you.

DR. RAO: Let's go on to Question Number 3.

DR. HWANG: As summarized in the Executive Summary, the co-primary endpoints developed a priori included a measurement of radiographic herniation rate designed to capture all disc herniations, both symptomatic and asymptomatic, in order to measure the device effectiveness at 24 months. Radiographic endpoints to evaluate device integrity, such as migration and disassembly, were also included to evaluate the device function, though positive outcomes occurred regardless of device integrity. In addition, the Sponsor reported results from an alternative primary endpoint developed post hoc that focused on symptomatic reherniations at 24 months. Please discuss the following:

a. Please discuss all appropriate endpoint(s) (both safety and effectiveness) for an annular closure device, and the control population, the time point(s) at which the endpoint(s) should be evaluated and whether these should be the same.

DR. RAO: Could we just maybe stop there? Yeah.

DR. HWANG: Yeah.

DR. RAO: Thank you.

So please discuss all appropriate endpoints, safety and effectiveness, for an annular closure device, and the control population, and the time points at which these endpoints should be evaluated and whether these should be the same for the device, as well as

control, is what I'm presuming.

Anyone from the Panel? Dr. Smith.

DR. SMITH: I think this, in my mind, the clinical problem we're trying to address here is a tough problem; it's someone with a large annular defect who gets a microdiscectomy done, and those who do clinical care for these patients, it's a hard problem because we know they have a high rate of reherniation, and when they come back with that second large disc herniation in the same spot, you're faced with the question, do I do a revision discectomy, which then has an even higher rate of a third reherniation, or do I do a definitive fusion?

And so in that light, it would seem to me the real endpoint that we're looking at, ultimately, is do patients that get this device have a lower rate of progressing to a definitive fusion of a motion segment, because that's the real clinical problem that we're trying to address here. All of the outcome measures and other issues aside, that's the big picture question in my mind.

DR. RAO: Dr. Elder and then Dr. Baron.

DR. ELDER: I mean, I agree with that assessment, and I think along those lines, particularly since this is a younger population, I don't think 2 years is an adequate endpoint for looking at this. If you're trying to look at how long you can prevent a 40-year-old from getting a fusion, I don't think having it occur at 43 or 44 for a control or treatment group makes a substantial difference, so I would like to see a longer-term follow-up to show a difference in that rate.

DR. RAO: Thank you.

Dr. Baron.

DR. BARON: I think a longer-term follow-up, meaning 5 years, is useful, but I disagree respectfully with Dr. Smith, where I don't think fusion is necessary -- necessarily

the endpoint of the device versus not the device. I do believe that multiple-revision surgeries carry a higher risk of things like durotomy, things like neurologic demise and neurologic deterioration, and whether they're fused or not, these things can still happen. Ultimately, the question is does a person with a Barricaid have less surgery than someone without one?

DR. RAO: Okay. Dr. Melkerson, with respects to Question -- with respect to Question 3a, appropriate endpoints for safety and effectiveness for an annular closure device, I think the Panel generally feels that appropriate endpoints and appropriate metrics for success of an annular closure device include avoidance of repeat surgery, avoidance of complications with subsequent operations, and avoidance of subsequent fusion, a subsequent need for fusion. And the Panel generally feels that a 2-year time point may be inadequate to assess all of these possible endpoints and that a longer period of time may be necessary to more accurately assess the eventual success of an annular closure device. Is that adequate?

MR. MELKERSON: A little further clarification. I think the last part of the question, when you're creating the discectomy, if I understand the device, it could potentially herniate somewhere else beside -- in other words, if you increase the pressure inside the disc, you could herniate elsewhere, whereas the control patient, you would expect potentially reherniation through the same defect. So I think that's -- and I'm looking over at David to make sure I'm understanding this correctly, that's where we were asking would be the same or different.

DR. HWANG: I think that that was a point of discussion. If the Panel doesn't feel that it's an issue, then that's okay, too. I think that all of those things are open.

DR. RAO: Yeah, I don't think -- I know that my sense is not that that was a substantial issue during the Panel deliberations in terms of trying to find a metric for

success of the device. I think the overall incidence of reherniation is certainly an issue and the need for repeat operations for that reherniation is an issue.

Dr. Sayeed.

DR. SAYEED: Yusef Sayeed, Dr. Yusef Sayeed.

Dr. Rao, I would also just add, you know, if the study, in the future, could determine better functional outcomes in terms of the things that we've already brought up in the meeting, i.e., return to work, return to play, in what ways are they working, are they going back to their old job. You know, although there are endpoints and ODI and VAS, you know, those are probably the minimum in terms of functional outcomes of VAS. You know, it's been debated in the literature at this point. But, you know, most of the major academic organizations are looking at real functional endpoints at this point versus just, you know, these surgical outcomes.

DR. DONSHIK: Dr. Rao?

DR. RAO: Yeah, Dr. Donshik.

DR. DONSHIK: Jon Donshik.

I hate to beat a dead horse, but forgive me. I think, in terms of -- I was looking at the safety. Does not device failure fall under that category?

DR. RAO: I think so.

DR. DONSHIK: And so perhaps that is another endpoint or metric that we need to look at in determining, you know, whether this device is safe.

DR. RAO: Yes. Yes, Dr. Hwang.

DR. HWANG: I was just hoping, also, for a little bit more discussion regarding the inclusion of both all reherniations or symptomatic or whether they're both sort of important for different reasons, what the Panel thought about that.

DR. SUBHAWONG: Ty Subhawong.

I think including all herniations is important because it's addressing the presumed functional mechanism of the device, whether there is -- whether or not there is morphologic evidence of reherniation of disc, which the device is supposed to lower that incidence. So whether or not it's symptomatic or not, that obviously has clinical importance, but from a mechanistic standpoint, just the morphology of the disc and whether it's reherniated or not, I think, is an appropriate endpoint.

DR. RAO: I think including all reherniations is important.

Someone had -- yeah, Dr. Elder.

DR. ELDER: Thank you. I agree that including all reherniations is important, but I think systematic, I mean, symptomatic reherniations are the most important thing to look at because we see lots of patients with tremendous pathology, but if it's not symptomatic, there's usually no reason to treat it. So I think that's really the critical thing to look at. But I think one point also to make is that it should be specified that the herniation or symptomatic herniation should match the radicular distribution of where the pain is coming from and not just that they have leg pain.

DR. RAO: I think, Dr. Melkerson, in further response to Question 3a, I think including all reherniations is important, but I think there's also a certain level of constraint that I and some of the Panel members feel in that we didn't have adequate identification of exactly how a reherniation was defined, and the one axial MRI slice we saw in a human being, I personally wasn't convinced that what was pointed out as a reherniation was actually a reherniation; it looked more like an inflamed nerve root. But I think it would be nice to see a little bit more clarity on axial MRI imaging on reherniation and identification of reherniations. I hope that's adequate because --

MR. MELKERSON: I think that's enough.

DR. RAO: -- I've run out of additional facts.

Okay, let's go to Question 3b.

DR. HWANG: So please provide specific criteria that you feel should be included in a definition of symptomatic recurrent lumbar disc herniation for the annular closure device and the control.

I think, specifically, taking into account that this would sort of -- the best way we can do this now is really to apply it with the information that we have, unless you feel that absolutely necessary, I guess, new clinical data be provided because, you know, we've been discussing, sort of, the clinical correlations, and that portion, so please keep that in mind.

DR. RAO: Okay, thank you.

So any specific criteria we should include or we should ask the FDA to include as they -- for us to define symptomatic recurrent lumbar disc herniation. Please try and categorize your answer in terms of metrics that you've already heard of during today's Panel discussion and maybe additional metrics that you'd like to see that might give you some definitive information on a symptomatic recurrent lumbar disc herniation in terms of how successful the device has been.

Yeah, Dr. Subhawong.

DR. SUBHAWONG: Ty Subhawong.

I think, if we're asked to provide recommendations as to what a symptomatic reherniation would be, you know, I would start with the reherniation has to have morphological evidence of being evident, or it has to be seen on MRI and it has to produce symptoms that would be expected with impingement on the nerve root, so radicular symptoms, those that we speak to, you know, fundamental criteria for my definition of recurrent herniation.

DR. RAO: Thank you.

Dr. Graf.

DR. GRAF: I think you'd have to clarify that, though, as we've been talking about -- you'd have to say that it would be a recurrent disc herniation on MRI imaging with clinically appropriate subjective complaints of lower extremity radiating pain in a clinically appropriate level, which is then corroborated by physical exam findings, which would also have to be clinically appropriate to that level.

DR. RAO: Dr. Smith.

DR. SMITH: I would add to that, that there should be a documented symptom-free interval, or if not symptom free, an initial decrease that is at least -- that meets the minimally clinically important criteria and the outcome measures we discussed. And then there should be an interval where that improvement is maintained, and then when there's a recurrence, it should be confirmed by imaging, as others have said, and I would agree that we should at least confirm it's on the same side. In an acute reherniation, I think clinically sometimes it can be hard to correlate with the specific nerve root at times, but we should at least be able to match the side of the reherniation with the side of the symptom exacerbation.

DR. RAO: Dr. Melkerson, with respects to Question 3b, specific criteria to try and isolate symptomatic recurrent lumbar disc herniation, I think the Panel generally feels that a number of things could be utilized to more accurately assess symptomatic recurrent lumbar disc herniations, including a symptom-free interval after the index operation; number 2, correlation of clinical findings with MRI findings; number 3, more emphasis on the MRI findings, including what Dr. Katz has talked about previously, which is MRI findings with intravenous contrast, which would be new and has not been done in the study so far; number 4, I think we have to re-include the VAS leg scores to get a better -- to try and better isolate recurrent leg pain as part of the symptomatic recurrent disc herniation picture. Is that adequate?

MR. MELKERSON: That is adequate, thank you.

DR. RAO: Question 3c.

DR. HWANG: So lastly, while both a secondary discectomy and a secondary procedure that results in a supplemental fixation or fusion are typically counted as failures, should they be given equal weight in discussing risks accrued from implanting a device?

DR. RAO: Anyone? Dr. Elder.

DR. ELDER: I think this goes back to our discussion a few minutes ago, that I think they both are -- should be viewed as issues, but I think a fusion is a more serious issue.

DR. RAO: Yes, Dr. Kim.

DR. KIM: Yeah, I agree with Dr. Elder. We do not know what's the impact, future impact. This could cause like a lumbar -- lead to lumbar fusion because that shows higher lumbar fusion at the Barricaid group. It should include as a risk.

DR. RAO: Okay. With respect to Question 3c, Dr. Melkerson, I think the Panel generally feels that both repeat discectomy as well as other types of procedures, including fixation and fusion, are both failures. To some degree, what's done may depend on the mode of failure of the index operation. So if there's a device extrusion, for example, with some destruction of bone, then that might necessitate a fusion versus just a recurrent disc herniation issue. So I think giving them equal weight is not necessarily accurate, and it may depend on the individual scenarios for each patient. Is that adequate?

MR. MELKERSON: Yes, it's adequate.

DR. RAO: Okay, I think that was it in terms of the non-voting questions, correct?

(Off microphone response.)

DR. RAO: Are we taking a break now, or are we going straight through? We're going straight through?

UNIDENTIFIED SPEAKER: Yeah.

DR. RAO: So at this time the Panel will hear summations, comments, or clarifications from the FDA, and the FDA has 5 minutes to make these summations.

MR. MELKERSON: The FDA doesn't --

DR. RAO: The FDA. The FDA.

DR. McGIRT: Dr. Rao -- oh, sorry.

MR. MELKERSON: Dr. Rao, the FDA has no --

DR. RAO: Has no comments. So you're back up.

(Laughter.)

MR. STIEGMAN: Yes.

DR. RAO: Thank you.

MR. STIEGMAN: Dr. Matt McGirt will provide a summation.

DR. McGIRT: On behalf of the Sponsor, Mr. Chairman, the rest of the panelists, the FDA, the public attendees, thank you for the opportunity for us to present the trial results today and your time, and I think the discussion has been really insightful, and hopefully, we've addressed some of the concerns and answered the questions.

Just to summarize a lot of what you've heard today, you know, I trust the trial design. It's as good or is better than anything we have in orthopedic implant trials to date, and I trust the evidence that it generates. The patient demographics and disease characteristics of this trial match that in the U.S. literature. The pain thresholds which led to the index discectomy surgery, which led to the decision to reoperate, and for endpoint classification matched that which were recorded, matched that of the literature in the U.S. as well. I think this is a representative study population.

The composite endpoint that was rigorous, and used and defined a priori, was really designed to guard against any potential bias that may creep into an unblinded study, such as the decision to reoperate or definition of symptomatic reherniation, as any bump in ODI

or VAS that goes untreated or unclassified in secondary endpoints meet the criteria for the primary study endpoint failure; again, a composite endpoint, a priori, which was proven to be superior with Barricaid.

So when I look at this trial personally, as a clinician, I see a number of strongholds that build my confidence that the superiority we see here is not artifactual or biased or confounded. No matter how you look at the endpoints, primary or secondary, a priori or post hoc, superiority demonstrated in each of those. So that builds my confidence to trust the data I see today, and I certainly believe it is accurate data.

There really has never been a controlled study to date to accurately define the incidence and practice of large defects. Some of the panelists mentioned that today, and I think that's been one of the great discoveries in general practice that this trial, once published, will demonstrate. And so I believe, actually, that the incidence of large annular defect discectomy is a little bit larger than previously realized, particularly when you start to actively measure it.

But you know what? Maybe in the case that the incidence or the prevalence here in the U.S. of large annular whole discectomy might be a little bit less, but the Sponsor really is not claiming or indicating this device for all discectomy; it's only indicating it for folks that after a standard-of-care discectomy is performed, a large defect is left, and in some surgeons' hands in the U.S., that might be a minority of their practice, and others, it might be a larger subset. Either way, this device is only indicated in those situations and is not overreaching, and I personally believe that's appropriate and over-conclusions were not drawn here today.

When you look at -- when I look at the net sum of benefits and risks in these slides here, the net sum of total benefits outweighs the net risk at 2 years, and so I feel that really justifies "Is this a care improvement technology?" The net sum, I think, is a better outcome

for patients. You know, and there's been some discussion about 3, 4, and 5 years out; yes, all patients passed 2, and then the statistical power begins to drop, particularly at 4 and 5 years. But I wanted to, as a clinician, not a statistician, wanted to draw a point of clarity that if you see here in the slide, the treatment gap, the delta or the efficacy of this device is not narrowing. The statistical power for which the conclusions are drawn, as you'd expect, as those who pass 4 and 5 years dwindle, the statistical significance dwindles a little bit, but we're seeing no evidence of real convergence of the treatment effectiveness, if you look at these graphs or the actuary data.

And yes, the vast majority of effect is seen in the first 2 years, but that is exactly what we expected a priori. It is when recurrent disc herniation occurs. So yes, it is confirmatory for how the device is designed to be meaningful in patients. It's not meant to dramatically change reherniation at 5 years; reherniation happens, we know, in the first 2 years. So yes, we see the vast majority of the device benefit at 2 years as expected, validating, in my opinion, its mode of action and purpose. The question is, do we see unexpected side effects or tradeoffs Year 3, 4, 5 that negate the health benefit in the first years, and I believe the evidence speaks for itself that we do not.

Downstream care, such as reoperation or fusion or even accurate diagnosis of reherniation on advance imaging, are not complicated by the presence of a preexisting Barricaid device. I wish we had a better way to view the MRI here on the screen today, but as panelists mentioned today, today's MRI scans are really good, and this mesh does not create artifact that disallows us to see a change in recurrent or nerve root compression in the face of recurrent radiculopathy, in my opinion.

With regard to these EPCs, again, just to try to summarize here today, we are seeing radiographic endplate changes which overall stabilize. The subset that the FDA brought up today, rightfully so, right, that are mesh proximate changes with subsidence, referred to by

the FDA as lytic, actually show the greatest size stabilization in the last few years in subset analysis. Edema is reducing on MRI, we're seeing some sclerotic bone rimming around those lesions, and in fact, we're seeing a little bit of bone formation around the device, again, flexion-extension data showing that we don't see autofusion at 2 years in the close to 170 patients at 5 years, so it's not an autofusion process. But all of that, as clinicians, suggest a stabilizing process, not a runaway lytic inflammatory process. All of those characterizations discussed today support a stabilizing process at that motion segment.

With 169 patients, sure, it's 25% of the cohort, but with 169 patients and 675 EPCs followed 5 years and none of them associated with a clinical event or sequelae at the 5-year time point, I personally am satisfied. I don't think that with that size of events that are followed by the study at 5 years, that they're going to start turning into fractures or a listhesis instability, back pain issues requiring fusion at 6 and 7 years. To the eye test and quantitatively, it seems to be a stabilizing process, in my opinion as a clinician.

So I believe the Sponsor has generated evidence to support this novel device. It's much needed to fill a morbid gap in discectomy care. And on behalf of the Sponsor, thank you all again very much for your time today.

DR. RAO: Thank you, Dr. McGirt.

DR. McGIRT: I believe Dr. Golish wanted to say a few words.

DR. RAO: Before -- go ahead, Dr. Golish.

DR. GOLISH : Yeah, I appreciate Dr. McGirt addressing the thoughtful comments of the Panel all day, head on. I would like to say that my personal enthusiasm for being here today relates to the fact that this Sponsor has endeavored to do three extraordinary things. The first is conduct the highest resolution, most detailed, and comprehensive study of the pathophysiology of herniated disc and its microsurgical treatment irrespective of any medical device, and in doing so, it's not surprising to discover fundamentally new things

which have been discovered, and in doing so, they have permanently contributed to our understanding of this important disease process.

But the second is to offer the Panel the highest level of scientific evidence around evidence-based medicine in doing a superiority design relative to a gold standard surgical control. On numerous occasions, this Panel has been asked to interpret non-inferiority studies with all the difficulties, complexities, and nuances of two-arm non-inferiority studies without a control arm, which is a third arm. On occasions, this Panel has been asked to consider superiority studies but relative to nonsurgical control, which is relatively poorly controlled usual care, not isolating the placebo effect. So in doing a superiority study relative to a surgical gold standard control, that's a very high level of evidence for this Panel to consider.

But then the final thing is really patient focused and taking what we all know to be a very good operation for appropriately indicated patients and attempting to make it better for those high failures; they've done so in isolating a small, relatively at-risk subpopulation. This is in contrast to other sponsors who have sought labels that indicate the entire operative population or even newly indicated populations in isolating the at-risk subpopulation. This attempt to improve the care for those patients high to fail speaks to both patients and surgeons alike.

Thank you.

DR. RAO: Thank you, Dr. Golish.

Before we proceed to the vote, I'd like to ask our non-voting members, Ms. Rue, our Consumer Representative; Ms. Starowicz, our Industry Representative; and Ms. Schwartzott, our Patient Representative, if they have any additional comments.

Let me start with you, Ms. Rue.

MS. RUE: Thank you. This is Karen Rue.

I want to commend the Sponsor for the presentation they did and affecting the quality of life of this population group, but I do have concerns because of this population group, the changes in the endplate that they talked about, the recurrent surgeries and the quality of life issues for the different demographics that weren't explained, and I think if we think about putting this in a 21-year-old and not knowing what they're going to look like when they're 60 years old, I think we just need to do a little bit more studying and expand the time frame or the duration of the study.

Thank you.

DR. RAO: Thank you, Ms. Rue.

Ms. Starowicz.

MS. STAROWICZ: Sure. I think a lot of the points have been said and emphasized already, but again, just I wanted to commend both FDA and the Sponsor for conducting a very thorough, what appears to be a very thorough analysis, significant follow-up rates not only at the 2-year but certainly, as I mentioned earlier, substantial follow-up out to 5-year, just an exhaustive imaging data and analysis and use of CT scans as well, too, at all time points. So, again, just wanted to just -- just appreciate the vast amount of information that's before the Panel today.

And also, I'm assuming Commander Anderson will be going through the standards, right, for the threshold for PMA approval, but really just wanted to emphasize, you know, the reasonable assurance of safety and efficacy, not safety and efficacy beyond all shadow of a doubt, but reasonable assurance and a favorable benefit-risk profile.

Thank you.

DR. RAO: Thank you, Ms. Starowicz.

Ms. Schwartzott.

MS. SCHWARTZOTT: I, too, appreciate the work that's gone in on all sides, especially

with the Sponsor. They've definitely shown that their acute patients have better results over the control, especially with the 2-year benefit up to 5 years. But I really have a lot of concern for the long-term safety of the device. If the average age of the person is -- or the patient is in their 40s, we have a long time to live with this device. If it's proven that the repeated reoperation leads to numerous problems, is this just a short-term fix? I'm inclined to lean towards approving the product even though I'm not a voting member, but I think that further study needs to go into it.

Dr. Baron's comments, does a person with Barricaid have less surgeries to go through than one without, and that really struck a chord with me because it definitely seems to benefit over patients that are just getting the discectomies. So, again, I think future study needs to happen, but yet, this is an area that hasn't been focused on before, and it's very promising.

DR. RAO: Thank you, Ms. Schwartzott.

I think we're now ready to vote on the Panel's recommendations to the FDA for the Barricaid Anular Closure Device by Intrinsic Therapeutics. The Panel is expected to respond to three questions relating to safety, effectiveness, and benefit versus risk. Commander Anderson will now read three definitions to assist in the voting process. Commander Anderson will also read the proposed indication for use statement for this device.

Commander Anderson.

CDR ANDERSON: Hi, good evening. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket applications, PMAs, that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be

supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that the device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of a target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence, as defined in 21 C.F.R. Section 860.7(c)(2), is evidence from well-controlled investigations, partially controlled studies, and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and reasonably be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following indications for use, and they're welcome to put it up on the screen: The Barricaid is intended to be implanted following a limited discectomy to prevent reherniation and the reoccurrence of pain or dysfunction. The Barricaid is indicated for patients with radiculopathy (with or without back pain), a posterior or posterolateral herniation, characterized by radiographic confirmation of neural compression using magnetic resonance imaging, and a large annular defect (e.g., between 4-6 mm tall and between 6-12 mm wide) post-discectomy, at one level between L4 and S1.

Just for your information for the panelists, you can vote on your microphone; that's how you vote. Okay. So, Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three questions. I will read the voting questions.

Voting Question 1 reads as follows: Is there reasonable assurance that the Barricaid is safe for the indication for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

(Panel vote.)

CDR ANDERSON: Thank you.

Voting Question Number 2: Is there reasonable assurance that the Barricaid is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

(Off microphone comment.)

CDR ANDERSON: It's not working?

(Off microphone response.)

CDR ANDERSON: Is it working now? Okay, thank you.

(Panel vote.)

CDR ANDERSON: It looks like we're waiting for two people to vote. You can abstain, if you want to.

(Pause.)

CDR ANDERSON: Voting Question Number 3: Do the benefits of the Barricaid outweigh the risks for use in patients who meet the criteria specified in the proposed indications?

Please vote now: yes, no, or abstain.

(Panel vote.)

CDR ANDERSON: The votes have been captured, and I will now read the votes into the record.

On Question Number 1, the Panel voted 5 yes, 9 noes, 0 abstains that the data shows reasonable assurance that the Barricaid Anular Closure Device by Intrinsic Therapeutics is safe for patients who meet the criteria specified in the proposed indications.

On Question 2, the Panel voted 12 yes, 1 no, 1 abstain that there is reasonable assurance that the Barricaid Anular Closure Device by Intrinsic Therapeutics is effective for use in patients who meet the criteria specified in the proposed indications.

On Question 3, the Panel voted 5 yes, 8 noes, 1 abstain that the benefits of the Barricaid Anular Closure Device by Intrinsic Therapeutics outweigh the risks for use in patients who meet the criteria specified in the proposed indications.

The three voting questions are now complete. Thank you.

DR. RAO: Thank you, Commander Anderson.

I will now ask the Panel members to discuss their votes. I'd like to go around the table and have each Panel member state how they voted on each question so it can be entered into the public record. Please also discuss the reasoning for your vote. If you answered no to any question, please state whether changes to labeling, restrictions on use,

or other controls would make a difference in your answer.

Let me start with Dr. Finnegan.

DR. FINNEGAN: So I voted no on safety. I think there are a couple of reasons. One, their pathologist showed pieces of the fiber, of the material in their fibrous tissue in the defects, and that's a little bit concerning. I have enough gray hair to have seen people swear that things are not going to be a problem that become a problem.

Secondly, it appears that the device at the junction with the plate has some issues and appears to separate, and I think more importantly, it migrates in the wrong direction, and that is definitely of some concern.

I abstained on the effectiveness because basically, it's 50%, and I'm not sure if that's a yes or a no. And then I think they need to do some more work before you can say that the benefits outweigh the risks.

DR. RAO: Thank you, Dr. Finnegan.

Dr. Graf.

DR. GRAF: I voted yes for the first voting question. I know there was questions about the endplate changes, although it wasn't, in my mind, clinically relevant.

To Question Number 2, I also voted yes, that there was reasonable assurance that it was effective at least at the set time point of 2 years, which was what we were asked to vote on.

And for 3, I also voted yes.

DR. RAO: Thank you, Dr. Graf.

Dr. Donshik.

DR. DONSHIK: With respect to the first question, I voted no. I'm concerned about the lesions, I'm concerned about the device failures.

Second question, I did vote yes. I think it is effective. Is it effective enough? That

one I don't know, but I wasn't asked that.

And based on my concern about Question Number 1, I voted no that it was -- the risks are too great and do not outweigh the benefits.

DR. RAO: Thank you, Dr. Donshik.

Dr. Subhawong.

DR. SUBHAWONG: Yeah, Ty Subhawong.

For Question Number 1, I voted yes, that it is reasonably safe because I think the major concerns kind of center around a lot of these endplate lesions, which there's some theoretical concern that they're -- these could be harbingers of subsequent device failure or increased failure rates with disc reherniation. I thought the number of lesions observed was sufficient to reassure me that there was nothing catastrophic about these, and I think, like, a post-approval study to follow these lesions for now would probably be prudent, but it wasn't enough to convince me that the device wasn't safe.

For Question Number 2, I voted yes, that it was effective. I think the Sponsor showed pretty rigorous data proving that over the time period of the study, that the Barricaid implanted arm was superior for multiple endpoints, both radiological and clinical, compared to control.

And then for Voting Question Number 3, do the benefits outweigh the risk, I thought that in this case, again, based on the safety profile of the implant and the efficacy demonstrated compared to control, there's a number -- that the device was beneficial. And I wanted to note that also the number needed to treat in the study was around 5 to 10, which is pretty good for a low number needed to treat for effect.

DR. RAO: Thank you, Dr. Subhawong.

Dr. Evans.

DR. EVANS: I voted no on safety, yes on effectiveness, and no on benefits

outweighing the risks.

For safety, I think there's an important distinction between saying we've seen -- we've looked at the data and we haven't seen anything yet versus an assurance of safety, particularly in light of the signs of the lesions that we've seen. I think we need to see longer-term outcomes, particularly given the age of the patients here.

For effectiveness, I thought that the reherniation results were robust. I had some issues with aspects of the trial, but I think the magnitude of that effect was large enough to show effects on reherniation.

I voted no on the benefits outweighing the risks partly because I would like to see -- I thought that Dr. Sayeed made a very good comment about it. I would really like to see information about how it improves function or how patients feel with regard to pain and those sorts of things, and in the label, there's talk about recurrence of pain and dysfunction, and I didn't really get overwhelmed from that perspective. So that's it.

DR. RAO: Thank you, Dr. Evans.

Dr. Kim.

DR. KIM: I voted first question no. Concerning the lytic regions, we don't know what exactly it is and then also what is the potential impact. So particularly when you think about we perform surgery on young generation, like 20, 30 years old, we don't know what's going to happen in 40 years, so I voted no.

Question Number 2, I voted yes. I think it is a -- study showing 2 years of benefit obviously. I believe this is -- when you do a procedure, usually we do not follow more than 2 years. I'm kind of surprised they did 5 years of follow up, so I voted yes.

I vote Number 3 as a no. As I said, safety is my concern, so I voted no.

DR. RAO: Thank you, Dr. Kim.

Dr. Katz.

DR. KATZ: Lee Katz.

On Question Number 1, I voted no. I believe that I really didn't understand what the reaction was, and I think the Sponsors could've done a better job with presenting more pathology that could've been more convincing, and I think, also, in terms of the imaging, there could have been some better imaging.

On Question Number 2, I voted yes. I thought that they presented material that I thought demonstrated that the Barricaid was effective.

And on Question Number 3, I voted no, basically, again, because of Question Number 1, which I felt was a safety issue.

DR. RAO: Thank you, Dr. Katz.

Dr. Wang.

DR. WANG: Marjorie Wang.

I voted yes on Question 1 based on the adverse events profile, and although there was a higher incidence of the EPLs, that these did not appear to have clinical significance, and finally, a comparison of clinical outcomes, which was similar between device and control.

On Number 2, I voted yes. That was based on the reoperations, 2 years, both on the imaging and the first definition of recurrence, as well as symptomatic recurrence.

And for Number 3, I voted yes based on 1 and 2.

DR. RAO: Thank you, Dr. Wang.

Dr. Smith.

DR. SMITH: On Question 1, I voted yes. I felt within the data presented, there was a reasonable assurance regarding safety, that there obviously was a lot of discussion of the endplate lesions and they may require some type of post-surveillance, but I felt within the definition of reasonable and the data presented, I voted yes, that it was safe.

Question 2, I voted yes. The data show it was a well-designed study and showed a clear clinical effectiveness within their study, so I voted yes for Question 2.

And then Question 3, I voted yes.

DR. RAO: Thank you, Dr. Smith.

Dr. Baron.

DR. BARON: For Question 1, I voted no, simply because of the high rate of breakage of the device, the high rate of migration, and also the unknown nature of the lesions, especially in this young population, especially that most of the people undergoing this surgery will probably be in their 30s or 40s, and we don't know what's going to happen years down the line.

In terms of Question 2, I voted yes, I do believe the Barricaid is an effective device in preventing reherniation.

In terms of Question 3, I do believe, in a selected group of patients, the benefits do outweigh the risk, providing the patient is counseled that there's a lot unknown and that this may pose a risk in the future. They should, in my opinion, be able to get this device.

DR. RAO: Thank you, Dr. Baron.

Dr. Elder.

DR. ELDER: To the first question, I voted no. I thought it was a young population, there is an incomplete characterization of the endplate lesions, and also the high number of device failures, as has been stated.

To Number 2, I voted yes, that I thought the Sponsor did show that there was adequate efficacy in this group.

To Number 3, I voted no due to my safety concerns, as well as some concerns with study design, such as no correlation or clinical correlation with disc herniation, as well as lack of consistent criteria for reoperation. But I think a lot of my safety concerns could be

addressed with longer-term follow-up data, and both those answers could be changed to a yes.

DR. RAO: Thank you, Dr. Elder.

Dr. Weisbrode.

DR. WEISBRODE: I voted yes on Number 1 based on language and data presented. We were asked to be reasonable assurance, not without a doubt, and I thought they provided reasonable assurance. And also, on the language of the possible, we discussed a lot of possible complications from the endplate lesions, but the language we were required was probable, probable problems, and so I don't think we came up with probable endplate lesions issues.

I voted yes on Number 2, as did others, based on the efficacy, the data presented, and the data showed about the clinical improvements.

In terms of Question 3, I abstained. I considered myself as a patient, and I just damn wasn't sure whether I was going through with it or not.

DR. RAO: Thank you, Dr. Weisbrode.

Dr. Gilbert.

DR. GILBERT: Yes. So I voted no on Question 1 for many of the reasons that have described by Dr. Baron and Dr. Elder. The safety issues, I think many questions were raised, and I didn't have enough assurance that those safety issues had been adequately addressed.

In Question 2, I voted yes. I think the design of the study did demonstrate benefit, and actually, I commend the Sponsors for a very well-designed study.

And then in Question 3, because of my concerns with safety, I voted no.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Sayeed.

DR. SAYEED: First of all, I'd like to say I appreciate what Dr. Golish had talked about in his closing. It is very rare to see superiority analyses when it comes to medical devices, and I hope the FDA continues this trend on asking for a superiority analysis when we're looking at medical devices, instead of these non-inferiority studies.

So I voted no in terms of safety for many of the reasons that my colleagues have mentioned. You know, we just don't know the long term, the long-term safety in terms of the endplate lesions, and so I think that overarching, you know, problem is something that really needs to be addressed in future studies.

I did vote no in terms of efficacy. I didn't think that -- you know, when you compare effectiveness to the status quo or the empiric treatment, I didn't think it was any better; in fact, you know, when comparing the device, which may or may not increase the pressure in the disc which may cause a herniation either medially or laterally and you're back to the same problem that you had initially and the reherniation rate was very high, so in those terms, I voted no.

And then the same, so in terms of the benefit-risk ratio, based on those two.

DR. RAO: Thank you, Dr. Sayeed.

I'd like to thank the Panel. That was an outstanding discussion and outstanding questions raised by all Panel members. I'd like to thank the Panel for their attentiveness over a long and arduous day.

Dr. Melkerson.

MR. MELKERSON: I would just like to thank the Panel for their time, efforts, and deliberations, and the Sponsor for presenting their case and their device. And also to the review team for presenting the data that they did as well.

DR. RAO: Thank you. I was going to say the same thing. I'd like to thank the Sponsors for a lot of hard work, a very carefully put together proposal. I'd like to thank

them for the level of detail and for their attentiveness to the Panel's questions, so thank you very much for all your hard work. I'd like to similarly thank the FDA reviewers for their hard work and for their lengthy presentations today and their careful analysis of the Sponsor's proposal, which is what the FDA is mandated to do; you're looking after the best interests of our patients, so thank you very much. Thank you, all.

Dr. Melkerson, any final remarks?

MR. MELKERSON: Stay warm.

(Laughter.)

DR. RAO: I now pronounce the December 12th, 2017 meeting of the Orthopaedic and Rehabilitation Device Panel -- Devices -- adjourned.

Thank you. Have a good evening, everyone. Drive safe, travel safe.

(Whereupon, at 5:03 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

December 12, 2017

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter